University of California, Los Angeles

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

35 $9,098,175

b) The subject of research grants by academic discipline:

Cancer	= 16
Cardiovascular Disease	= 3
Engineering	= 1
Epidemiology	= 2
General Biomedical Science	= 3
Public Health, Public Policy, and Economics	= 5
Pulmonary Disease	= 4
Tobacco Use Prevention, Intervention, and Cessation	= 1

c) The relationship between State and Federal funding for tobacco research:

Other State	= 0
Federal	= $537,195

d) The relationship between each project and the overall strategy of the research program:

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

12 $2,942,235

g) The number and species of animals used in research:

Dogs	= 30/year
Mice	= 1,340/year
Rabbits	= 91/year
Rats	= 1,650/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

11 $2,870,863

Grant Recipient(s):

1. Aberle, Denise — Cancer
Advances in lung cancer detection with digital techniques
$276,730 (7/91-6/94)

2. Baldwin, Gayle — Cancer
The role of the macrophage in lung cancer
$215,007 (7/91-6/94)

3. Black, Alexander C. — Cancer
Nmyc oncogene expression in small cell lung cancer
$225,000 (7/90-6/93)

4. Dirksen, Ellen — Pulmonary
Control of mucociliary clearance in the respiratory tract
$404,950 (7/90-6/93)

5. Dubinett, Steven M. — Cancer
Local cytokine immunotherapy for lung cancer
$225,000 (7/90-6/93)

6. Economou, James — Cancer
Gene modification of human lung tumor-infiltrating lymphocyte
$152,816 (7/90-6/92)

7. Endoh, Kazuo — Gen Biomed
Acute and chronic nicotine treatment on gastric ulceration
$70,000 (7/90-6/92)

8. Enstrom, James — Epidemiology
Tobacco-related disease trends among 118,000 Californians
$254,000 (7/91-6/94)

9. Fogelman, Alan M. — Cardiovascular
Determinants of susceptibility to oxidized lipoproteins
$324,569 (7/90-6/93)

10. Gasson, Judith — Cancer
Smoking and leukemia: a molecular genetic approach
$334,253 (7/91-6/94)

11. Gil, Enrique — Pulmonary
Acute and chronic effects of tobacco and non-tobacco smoking
$35,000 (7/90-6/91)

12. Golub, Sidney H. — Cancer
Tumor infiltrating lymphocytes & pulmonary macrophages
$423,786 (7/90-6/93)

13. Gupta, Rishab — Cancer
significance of immune complexes in human lung carcinoma
$360,485 (7/90-6/93)

14. Guth, Paul — Gen Biomed
The mechanism of nicotine-induced gastric mucosal injury
$220,998 (7/90-6/92)

15. Hankinson, Oliver — Cancer
Cloning of two genes involved in tobacco carcinogenesis
$323,634 (7/90-6/93)

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

16. Hinds, William Engineering
Interaction of occupational aerosols and tobacco smoke
$192,878 (7/90-6/93)

17. Holmes, E. Carmack Cancer
Early detection of lung cancer with monoclonal antibodies
$874,781 (7/90-6/93)

18. Hser, Yih-Ing Pub Health
Long term patterns and consequences of tobacco use among narcotic addicts
$74,840 (7/91-6/92)

19. Ignarro, Louis Cardiovascular
Detrimental influence of NO on vascular/platelet functions
$288,188 (7/90-6/93)

20. Jarvik, Murray Pub Health
Black-white differences in menthol cigarette smoking
$332,114 (7/90-6/93)

21. Kaplan, Celia Pub Health
Factors affecting smoking initiation in young latina women
$149,821 (7/91-6/93)

22. Koeffler, H. Phillip Cancer
Lung cancer: p53 as a paradigm of tumor suppression
$474,876 (7/90-6/93)

23. Lehrer, Robert Pulmonary
Antimicrobial proteins of human alveolar macrophages
$71,549 (7/91-6/92)

24. Leung, Felix Gen Biomed
Cigarette smoke, nicotine & acid-induced duodenal injury
$311,797 (7/90-6/93)

25. Li, Virginia Intervention
Assessing organizational influence on chinese smoking
$75,000 (7/91-6/92)

26. Lill, Michael Cancer
Homeobox genes hematopoiesis and leukemogenesis
$70,000 (7/91-6/93)

27. Longnecker, Matthew Epidemiology
An idea for a cohort study of tobacco-related cancers
$73,439 (7/91-6/92)

28. Mody, Freny Cardiovascular
A metabolic mechanism of action of antiischemic agents
$225,000 (7/91-6/94)

29. Nimer, Stephen Cancer
Retinoic acid receptor expression in human lung cancer
$225,000 (7/90-6/93)

30. Sarna, LindaPub Health
Impact of nursing care on symptom distress & quality of life
$221,193 (7/91-6/94)

31. Schiller, Gary John Cancer
Stem cell transplantation for small&non-small cell lung cancer
$174,666 (7/90-6/93)

32. Shapiro, David Pub Health
Stress & smoking in natural settings: an ambulatory study
$489,885 (7/90-6/93)

33. Shau, Hungyi Cancer
Neutrophil cytostatic activity against lung tumor cells
$223,628 (7/90-6/93)

34. Slamon, Dennis J. Cancer
Studies of proto-oncogenes & growth genes in human lung cancer
$336,209 (7/90-6/93)

35. Ward, Susan A. Pulmonary
Carotid body amplification of exertional dyspnea in smokers
$367,083 (7/90-6/93)

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Source: https://www.industrydocuments.ucsf.edu/docs/mfv0000

AWARD # HI-63 AWARD PERIOD July 1, 1991 - June 30, 1992

PRINCIPAL INVESTIGATOR ELLEN R. DIRKSEN, Ph.D.

INSTITUTION University of California, UCLA School of Medicine

TITLE OF PROJECT Control of Mucociliary Clearance in the Respiratory Tract

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Chronic obstructive lung disease is symptomatic of smokers of long standing, due to the accumulation of mucus in the respiratory tract. The tissue that lines the respiratory tract is damaged by many of the compounds found in tobacco products, destroying the cells involved in mucus transport. We are studying two important regulatory mechanisms of these cells: 1) The control of the motion of the small, hair-like structures called cilia (hundreds of which are found on each ciliated cell of the airway lining), whose whip-like motion within the watery layer moves the more viscous mucus blanket floating above and 2) The ions (salt) that control the composition of the thick mucus layer and the watery layer (in which the cilia are able to function). The cells lining the airways also have small canals that open and close and through which salts can move from one side to the other of the lining. If either of these components (cilia and mucus) are not properly regulated, trouble ensues resulting in airway obstruction. We have found how ciliary activity can be controlled by the important ion, calcium, which acts as a messenger in many cell functions. We have shown that the mucus can act locally to increase ciliary activity by mechanically (its weight) disturbing the cells underneath. When this happens calcium channels (canals in the cell covering) open, allowing calcium to enter and increase ciliary activity. These cells also communicate with other cells by specialized bridges. Thus, the surrounding cells also increase their ciliary activity. Hormones arriving by blood vessels also affect ciliary activity. Thus we have both a local and general control of ciliary activity, increasing the rate at which mucus is being propelled towards the mouth, where it can be expectorated. At the same time, the ciliated and other cell types of the airway lining are selectively allowing salts to be released or withheld, thus controlling the height of the periciliary layer and, secondarily, the viscosity of the mucus. If too thick, the mucus has difficulty in being cleared from the airways. The study of calcium signalling and its effect on ion transport and ciliary beating provides an opportunity for selecting possible therapeutic approaches to alleviate lung disease.

AWARD # IKT110 AWARD PERIOD 7/1/90-6/30/93

PRINCIPAL INVESTIGATOR Steven M. Dubinett, M.D.

INSTITUTION UCLA School of Medicine

TITLE OF PROJECT LOCAL CYTOKINE IMMUNOTHERAPY FOR LUNG CANCER

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This study is designed to evaluate the ability of two naturally-produced proteins, interleukin 2 (IL-2) and gamma interferon (IFN), to decrease tumor growth in mice with lung cancer. We hypothesized that these substances (also called cytokines) would be more effective and less toxic if injected directly into the tumor rather than given intravenously. When directly injected into the tumor IL-2 was found to increase the tumor-killing activity of white blood cells within the tumor. We found that IL-2 given by direct injection into the tumor was more effective than IL-2 injected into the body distant from the tumor. Compared to the control group, in which all of the mice with lung cancer died, 25% of the mice were cured when IL-2 and IFN were used together. These studies bring us closer to using cytokines to more effectively fight lung cancer in humans.

AWARD # KT 64 AWARD PERIOD 7/1/90-6/30/93

PRINCIPAL INVESTIGATOR Alexander C. Black, M.D.

INSTITUTION UCLA School of Medicine

TITLE OF PROJECT N-myc Oncogene Expression in Small Cell Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project involves the characterization of N-*myc* oncogene expression in small cell lung cancer (SCLC). Oncogenes are normal genes involved in cellular growth or differentiation that are either mutated or abnormally expressed in cancer cells. In particular, *myc* family oncogene overexpression occurs in 10-40% of SCLC patients, and may be associated with chemotherapy resistance and a poorer prognosis.

Our initial studies have concentrated on defining the regulatory regions near the N-*myc* gene, called the promoter and enhancer elements that control gene expression. Over the last year, we have mapped two positive and three negative enhancer elements and identified a promoter area required for production of RNA. We have begun studies to determine whether cellular proteins bind to this minimum required promoter region.

We have also begun to characterize *myc* oncogene expression in SCLC cell lines. We currently have six SCLC cell lines, three of which overexpress a *myc* family oncogene by gene amplification (or increased numbers of the normal gene): one N-*myc*, one L-*myc* and one c-*myc*. We plan to compare the regions of the promoter of the N-*myc*-overexpressing SCLC line with two N-*myc*-expressing neuroblastoma cell lines: one that overexpresses N-*myc* by gene amplification (LAN-5), and one that overexpresses N-*myc* despite a normal number of N-*myc* genes (LAN-6). We are also beginning to accrue tissue from the cancers of SCLC patients to turn into cell lines and test for patterns of N-*myc* expression. We believe that these results represent important initial steps in our studies.

AWARD # RT62 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR James S. Economou, M.D., Ph.D.

INSTITUTION University of California Los Angeles

TITLE OF PROJECT Gene modification of human lung tumor infiltrating lymphocytes.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Human tumor infiltrating lymphocytes (TIL) are white blood cells found within solid tumors. These white blood cells or lymphocytes appear to have specific antitumor killing abilities not found among white cells circulating in the blood. These TIL can be grown in tissue culture and increased in number over 100-fold. When given back to the cancer patient, in some instances, they appear to localize specifically to tumor sites and to mediate the destruction of tumor.

Our research is designed to find ways of making these TIL better tumor killing lymphocytes. To do this, we are introducing new genes into these TIL in an effort to make them more effective in cancer therapy. We have selected a number of genes such as interleukin 1, 4, 6 and 7 which are capable of activating lymphocytes and helping them to grow better. We have demonstrated our ability to insert a number of these genes into human TIL and determining whether these TIL then acquire newer and more effective antitumor properties.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # FT 37 AWARD PERIOD July 1990 - June 1992

PRINCIPAL INVESTIGATOR Kazuo Endoh, M.D.

INSTITUTION Sepulveda VAMC – UCLA

TITLE OF PROJECT Acute and Chronic Nicotine Treatment on Gastric Ulceration

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

In the rat stomach, acute intragastric (i.g.) nicotine protects against mucosal injury, while acute intravenous (i.v.) nicotine or chronic i.g. nicotine aggravates mucosal injury. The purposes of the studies to date are to elucidate the mechanism of action of acute i.g. (studies 1 - 3), and i.v. (study 4) nicotine in modifying mucosal injury.

Study 1: We test the hypotheses that α-, β-adrenoceptor mechanisms or endogenous sulfhydryls compounds are involved in the effect of i.g. nicotine. By using specific antagonists, we find that α2-adrenoceptors mediate in the protective effect of i.g. nicotine possibly by a mucus-dependent mechanism. α_1, β_1, β_2 adrenoceptor mechanisms or endogenous sulfhydryls compounds are not involved.

Study 2: Nicotine has ganglionic stimulatory and inhibitory properties. We examine the hypotheses that i) ganglionic stimulation by i.g. tetramethylammonium (TMA) has an effect similar to i.g. nicotine, ii) ganglionic blockade by hexamethonium or mecamylamine abolishes the protective effect of i.g. nicotine. We find that i.g. TMA dose-dependently protects, suggesting that the ganglionic stimulatory property of nicotine plays a role in mediating its protective effect. Unexpectedly, hexamethonium and mecamylamine also protect, but the mechanism is unexplained at this time.

Study 3: We examine the relationship between regional differences in mucosal nicotine concentration (by ^{3}H-nicotine labeling), and the protective effect of i.g. nicotine. Nicotine protects the corpus mucosa but not the antral mucosa. A higher concentration of nicotine is demonstrated in the superficial corpus mucosa than the antral mucosa.

Study 4: We test the hypothesis that aggravation of gastric mucosal injury by i.v. nicotine is due to inhibition of gastric prostaglandin generation or impairment of injury-induced gastric hyperemia. We find that i.v. nicotine aggravates hypertonic saline-induced mucosal injury, impairs injury-induced hyperemia, but has no effect on mucosal prostaglandin generation.

AWARD # FT 42 AWARD PERIOD July 1, 1990-June 30, 1991

PRINCIPAL INVESTIGATOR Enrique Gil

INSTITUTION UCLA Medical Center

TITLE OF PROJECT Acute and Chronic Effects of Tobacco and Non-tobacco Smoking on Pulmonary Epithelial Permeability.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The rate of clearance of small molecules such as DTPA from the lung, has been found to be increased in tobacco smokers, probably as a result of injury to the cells forming the alveolar sacs. Like tobacco smoking, habitual use of marijuana is associated with symptoms of acute and chronic bronchitis and increased number of inflammatory cells obtained from lung fluid, suggesting that marijuana may also cause lung damage, although standard tests of lung function are usually normal. Assessment of permeability of the air sacs to technetium bound DTPA in habitual smokers of marijuana has not previously been performed. DTPA is radioactively tagged with 99mTechnetium in order to detect it with the use of special cameras.

The purpose of this study is to assess the effects of acute and chronic smoking of marijuana and/or tobacco when compared with normal nonsmoking subjects and to serve as the starting point for further studies concerning the effects of smoking on the alveolar epithelium (air sacs).

Up to date, 9 control non-smokers and 9 marijuana smokers have been studied and analyzed (2 studies per subject). The preliminary data indicate that 1) habitual smoking of marijuana alone increases the clearance rate of DTPA from the lung compared to nonsmokers and 2) smoking a single marijuana joint causes a further increase in clearance. These results suggest that habitual marijuana smoking causes subtle damage to the alveolar sacs which is acutely augmented by smoking a single marijuana cigarette. In addition, 10 tobacco and 10 tobacco/marijuana smokers are being studied in order to compare the effects of both substances and to assess the superimposed effects, if any, of the combined use of tobacco and marijuana on the lung clearance for DTPA.

AWARD # RT 322 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Alan M. Fogelman, M.D.

INSTITUTION University of California, Los Angeles

TITLE OF PROJECT Determinants of Susceptibility to Oxidized Lipoproteins

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Atherosclerosis accounts for a large number of deaths in the tobacco related diseases and is responsible for cardiovascular, coronary artery, and peripheral vascular disease. Our objective is to understand the initial events in atherosclerosis. It is our hypothesis that oxidation of blood fats results in an inflammatory reaction that leads to atherosclerosis. In general the blood fats of smokers are more susceptible to oxidation. However, some individuals seem to be relatively immune. Our preliminary results suggest that this immunity may be related to a genetically determined ability to induce enzymes that can detoxify the oxidized lipids.

AWARD # RT 206 AWARD PERIOD 7/1/90 to 6/30/91

PRINCIPAL INVESTIGATOR Sidney M. Golub

INSTITUTION UCLA School of Medicine

TITLE OF PROJECT Tumor Infiltrating Lymphocytes & Pulmonary Macrophages

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Lung cancer is the number one cause of cancer death in California. Conventional surgery and chemotherapy have had little impact on this statistic and alternative therapies are needed. Adoptive immunotherapy, an experimental treatment which uses the bodies own immune system to fight cancer, produces remissions in approximately 30% of patients with skin or kidney cancer. Unfortunately, patients with lung cancer respond poorly to the same regimen. Our objective is to recover and analyze immune cells from human lung and skin cancers (referred to as tumor infiltrating lymphocytes, or TIL) in order to determine why these two cancers respond so differently to immunotherapy. We hypothesize that lung cancer TIL contain different subpopulations of immune cells as compared to skin cancer TIL, that they recognize the tumor via different mechanisms, and that they are subject to unique immunosuppressive factors within the lung environment. To date we have analyzed TIL subpopulations from 4 patients with lung cancer and 3 patients with skin cancer. While there were no definite differences in the cell surface markers between the two groups, activated skin cancer TIL were significantly more effective in destroying cancer cells. TIL from skin cancer patients readily destroyed both skin cancer and other tumor cells, while lung cancer TIL were rarely effective at killing lung cancer cells. Work in this area is ongoing. We also observed that pulmonary macrophages, cells which are unique to the lung environment, suppress the proliferative and tumoricidal activity of TIL. Inhibition is a concentration dependent phenomenon and the number of pulmonary macrophages is increased several fold in the lungs of tobacco smokers. Our results suggest that pulmonary macrophages may play an important role in suppressing the immune response to lung cancer. We are currently investigating the mechanism(s) of PM-mediated suppression and methods of reversing it. The impact of our work will be to better understand the biology of the immune response to lung cancer. With this knowledge we hope to improve the utility of adoptive immunotherapy.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # RT 77 AWARD PERIOD July 1, 1990 to June 30, 1991

PRINCIPAL INVESTIGATOR Rishab K. Gupta

INSTITUTION University of California at Los Angeles

TITLE OF PROJECT Significance of Immune Complexes in Human Lung Carcinoma

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The main objective of this research grant is to develop immunoassay(s) that could identify individual who may be at high risk of developing lung cancer. It is proposed that this would be done by identifying molecules that are produced exclusively by lung tumor cells and that elicit at least humoral immune response in lung cancer patients. With the production of such molecules, it is hypothesized that the presence of antigen specific immune complexes (product of immune reaction between tumor antigen and corresponding antibodies) at a given point in time would indicate the presence of subclinical disease or normal cells that have transformed to premalignant condition. Results obtained from the conduct of this investigation validate the foregoing hypothesis to significant extent. Using a murine monoclonal antibody to a glycoprotein which is produced by a variety of solid neoplasms and not by normal cells a sensitive enzyme immunoassay has been developed. Analysis of serum samples from 65 lung cancer patients revealed that 43 (66%) were positive for the presence of tumor antigen specific immune complexes. These patients had disease on board at the time of serum sampling. The negative results in some of the patients (34%) could be due to the fact that their tumor did not express the glycoprotein antigen which is recognized by the murine monoclonal antibody used in the assay. Thus, emphasis will be placed on defining additional tumor antigens and developing new monoclonal antibodies in the future years. Subsequent analysis of sequential serum samples from some the patients revealed that their sera became negative for the antigen specific immune complexes as the disease progressed. This perhaps represents a situation of antigen overload in circulation where the amount of tumor antigen specific antibodies is not enough to result in adequate level of immune complexes.

AWARD # RT 282 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Paul N. Guth, M.D.

INSTITUTION Center for Ulcer Research and Education, UCLA

TITLE OF PROJECT The Mechanism of Nicotine-Induced Gastric Mucosal Injury

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Gastric ulcers occur more frequently, and heal less well, in smokers than in non-smokers. Nicotine is considered to be one of the components in tobacco responsible for this. The surface mucus cell, with it's overlying mucous gel layer and the supplying blood vessels beneath it, forms the first line of defense of the stomach against mucosal injury. This project's aim is to determine the effect of nicotine on this defense line's ability to protect against an acid challenge.

Significant Findings to Date: 1) While the acute administration of nicotine into a rat's stomach significantly increased the thickness of the mucous gel layer, chronic administration of nicotine in the drinking water for two weeks significantly decreased the thickness of the mucous gel layer. 2) Alcohol in an acid solution also significantly decreased the mucous gel layer and caused a very marked fall in intracellular pH of the stomach surface cell. Taken together, findings 1 and 2 suggest that the mucous gel layer helps protect the surface cell against an acid load and that chronic nicotine, by decreasing the thickness of the layer, may render the cells more susceptible to acid damage. Studies testing this hypothesis are underway. 3) The sodium-hydrogen exchanger in the gastric surface cell also was found to play a major role in the cell's maintenance of normal intracellular pH in the face of an acid load. When this exchanger was blocked by hexamethylamiloride, the cell's pH failed to recover from an acid load. The effect of nicotine on this exchanger is a fertile field for future studies.

AWARD # RT 244 AWARD PERIOD 7/1/90 to 6/30/91

PRINCIPAL INVESTIGATOR Oliver Hankinson

INSTITUTION Laboratory of Biomed. & Env. Sciences, UCLA.

TITLE OF PROJECT Cloning of Two Genes Involved in Tobacco Carcinogenesis.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to clone two genes affecting Ah receptor function. This receptor is involved in carcinogenesis mediated by a number of environmental and industrial toxins, including benzpyrene, a toxin present in cigarette smoke. In addition to benzpyrene, another significant toxin which exerts its toxicity through this receptor is dioxin.

Once the genes, or their representative cDNAs are cloned, they may be used to more fully study the role of this recepter in carcinogenesis. It is possible that they may provide a tool which can be used to predict those at high risk from exposure to the toxins and carcinogens in the work place or to predict those individuals most likely to acquire cigarette smokeing induced lung cancer.

The past year has been spent developing a system which will be employed to clone the genes involved in receptor function. These preliminary experiments indicate that our approach for isolating the genes is feasible, and have provided that biological reagents for doing so. We anticipate cloning the two genes within the next year of grant support.

AWARD # 1RT-7 AWARD PERIOD July 1, 1990 - June 30, 1993

PRINCIPAL INVESTIGATOR William C. Hinds

INSTITUTION UCLA School of Public Health

TITLE OF PROJECT Interaction of Occupational Aerosols and Tobacco Smoke

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This study seeks to answer specific questions concerning the interaction of occupational aerosols and tobacco smoke. It is an experimental study designed to measure the extent to which airborne dust particles found in the workplace become coated with tar during smoking, and the effect of these coated particles on the dose of tar depositing in different regions of the lung. Because most smoking induced lung cancers originate in the respiratory airways and most of the tobacco tar deposits in the gas-exchange region of the lungs, these coated particles, which deposit preferentially in the airways, represent a potentially important source of tar exposure to the airways.

Progress to date includes the design, fabrication, and calibration of a dual cigarette smoking machine, exposure chamber, and sequencer to simulate human smoking. Cesium sulfate particles are used to simulate workplace dust particles, because this material is not found in tobacco or tobacco smoke and it is stable at the temperature of a burning cigarette. Five analytical methods to measure microgram quantities of cesium sulfate have been evaluated. The two most promising methods are undergoing experimental verification.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # 1RT 93 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR E. Carmack Holmes, M.D.

INSTITUTION University of California at Los Angeles

TITLE OF PROJECT "Early Detection of Lung Cancer with Monoclonal Antibodies"

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of the Southern California Early Detection Lung Cancer Program is to investigate the ability of newly developed monoclonal antibodies, to detect lung cancer in its earliest stages when it is almost universally curable. Preliminary studies at the Johns Hopkins Hospital using these two monoclonal antibodies indicate that these antibodies will aid in detecting lung cancer eighteen to twenty-four months before it is detectable by other techniques. This technique merely requires that the patient cough sputum into a container. The cells contained in the sputum are then examined by routine cytologic techniques and also with the new monoclonal antibodies. Patients with high risk for lung cancer are being screened in this fashion. The patient population includes those with a history of heavy smoking, patients with a history of resected lung cancer and patients with a history of head and neck carcinoma.

This program is part of a national program in which several universities across the United States are participating. The Statistical and Operations offices are at the Johns Hopkins Medical School and this institution is coordinating this nation-wide research program.

Lung cancer is the number one cancer killer in the United States with over 150,000 deaths each year. The successful application of these monoclonal antibodies techniques to the evaluation of sputum cytology could result in a significant increase of the cure rate of this disease.

AWARD # 1RT 33 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Louis J. Ignarro

INSTITUTION University of California, Los Angeles

TITLE OF PROJECT Detrimental Influence of NO on Vascular/Platelet Functions

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Nitric oxide (NO) is present in abundance in tobacco smoke and in polluted air. The principal objective of this research is to ascertain the mechanism by which NO causes certain tobacco-related cardiovascular diseases such as coronary artery disease, high blood pressure, and blood clotting disorders. The goals of this research are to determine the influence of NO on coronary and pulmonary blood vessel function and on platelet function. We have shown that NO produces beneficial actions such as lowering the blood pressure, and preventing thrombosis or blood clotting. We then showed that our own cells manufacture NO. Thus, NO is found not only in tobacco smoke and polluted air but also in our cells. The hypothesis forwarded is that excess amounts of NO are detrimental to health by turning off the body's capacity to produce its own NO, thus leading to pathological situations resulting from NO deficiency. Excess NO may cause a desensitization to the beneficial actions of NO and thereby lead to impaired function. The initial significant findings of the research are: (1) Although normal amounts of NO cause activation of guanylate cyclase, the enzyme responsible for formation of cyclic GMP, excess NO causes enzyme desensitization. Thus, cellular cyclic GMP formation is impaired after exposure to excess NO. Since cyclic GMP mediates the beneficial cellular actions of NO, decreased cyclic GMP formation could lead to impaired cellular function such as vasoconstriction, blood clot formation, and hypertension. (2) Excess NO causes desensitization of the enzyme NO-synthase, which is responsible for the formation of NO from an amino acid called arginine in most cells. Thus, any turning off of NO-synthase by excess NO could lead to similar pathological disorders. (3) In a collaborative study we found that injection of known inhibitors of NO-synthase (structural analogs of arginine) causes a marked increase in blood pressure, which is prevented by treatment of the animal with excess arginine, which overcomes the inhibition. Thus, a decrease in normal NO formation can be quite detrimental to the health of the animal.

AWARD # 1RT 87 AWARD PERIOD FY 90-91

PRINCIPAL INVESTIGATOR Murray E. Jarvik, M.D., Ph.D.

INSTITUTION University of California, Los Angeles

TITLE OF PROJECT Black-White Differences in Menthol Cigarette Smoking

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Is smoking menthol cigarettes associated with higher rates of lung cancer than smoking regular cigarettes? If so, why? These questions arose because 75% of Black male smokers are known to smoke menthol cigarettes, compared to 23% of White male smokers, and because Black males have higher rates of lung cancer than White males although Black male smokers smoke fewer cigarettes daily than White male smokers. To answer these questions, we are conducting face-to-face interviews with recent lung cancer cases in Los Angeles and comparing them to healthy controls. We have initiated 5 laboratory experiments which test the hypothesis that menthol acts as a local anesthetic, permitting greater exposure to the tar and nicotine in cigarette smoke. Four were 2-trial experiments using a modified rapid-smoking procedure. The first two experiments (N=28) required that subjects smoke 40cc puffs at 15 second intervals until they could not continue. In the first experiment subjects smoked their own cigarettes in both trials and in the second they smoked menthol cigarettes in one trial and regular cigarettes in the other. Contrary to prediction, menthol smokers smoked fewer puffs than did the regular smokers. Unexpectedly, the differences between menthol smokers and regular smokers disappeared on the second trial; menthol smokers smoked more puffs and regular smokers smoked fewer puffs on trial 2 than on trial 1. Also contrary to prediction, regular smokers took equal numbers of puffs from regular and menthol cigarettes as did menthol smokers. To see if the predetermined puff volume in the first 2 studies explained these surprising results, in experiment 3, 10 menthol smokers and 10 regular smokers smoked whatever volume they wanted (0-96cc). Contrary to prediction, all smokers inhaled a greater volume of smoke when smoking regular cigarettes than when smoking menthol cigarettes. The unusually high puff volumes reported in study 3 led to a fourth experiment. It involved 12 menthol smokers and 10 regular smokers and found,as expected, that the decline in "coolness" and the increase in irritation typically found during the smoking of a menthol cigarette were steeper in the higher puff volume (64cc) than in the lower puff volume (40cc) condition. More detailed smoking topography data (e.g., puff volume, etc.) are currently being collected in study 5, in a sophisticated pulmonary laboratory, from White and Black smokers smoking menthol cigarettes and regular cigarettes the way they would normally smoke. The questionnaire for the 3-year face-to-face interviews has been pilot-tested and is being administered to lung cancer cases drawn from Los Angeles hospitals and to healthy controls.

AWARD # 1RT370 AWARD PERIOD 1990-1993

PRINCIPAL INVESTIGATOR H. Phillip Koeffler, M.D.

INSTITUTION UCLA

TITLE OF PROJECT Lung Cancer: p53 as a paradigm of tumor suppression

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

A group of genes known as tumor suppressor genes appear to constrain the unlimited proliferation of normal cells. Alteration of these tumor suppresser genes can result in unfeathered growth of cells resulting in neoplasia. One of the major tumor suppresser genes is p53. We sought to determine the role of p53 mutations in lung cancer and to determine the normal function of p53 in order to better understand the alterations of p53 that occur in lung. We analyzed 41 tumors for p53 mutations and found that 14 tumors had mutations of the p53 gene. In addition, we did experiments to look at the normal function of p53 and found that it could act as a transcriptional activator (a protein that can turn on the expression of other proteins). Furthermore, we found that mutations of p53 can alter the ability of p53 to behave as a transcriptional activator.

Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

2023471124

AWARD # RT 80 AWARD PERIOD July 1990 - June 1993

PRINCIPAL INVESTIGATOR Felix W. Leung, M.D.

INSTITUTION Sepulveda VAMC – UCLA

TITLE OF PROJECT Cigarette Smoke, Nicotine & Acid-Induced Duodenal Injury

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purposes of ongoing experiments are to determine the mechanism of the adverse effect of intravenous nicotine on the gastrointestinal (particularly the duodenal) mucosa in experimental animals (rats). Study 1: Validation of the pulsed Doppler flowmetry (PDF) for the assessment of duodenal vasoconstriction. Simultaneous duodenal mucosal blood flow by hydrogen gas clearance (HGC) and superior mesenteric artery blood flow (a measure of duodenal blood flow) by PDF are obtained in rats subjected to graded levels of hemorrhagic hypotension. We find a significant linear correlation between HGC and PDF, suggesting that PDF may be adequate for demonstration of changes in duodenal mucosal blood flow. Study 2: Demonstration of dose-related increase in intestinal hyperemia by HCl. Intestinal blood flow is monitored by PDF (superior mesenteric artery flow). We find a dose-related increase in peak intestinal hyperemia induced by 0.01 N to 0.1 N HCl. Study 3: Validation of changes in duodenal ^{51}Cr-EDTA clearance as an index of acid-induced duodenal damage. We find a significant dose-related increase in duodenal Cr^{51}-EDTA clearance when 0.01 N to 0.1 N HCl is perfused through an isolated segment of duodenum. Study 4: We test the hypothesis that the effect of intravenous nicotine may be mediated by an effect on gastroduodenal prostaglandin generation. We find that intravenous nicotine in doses that aggravate gastroduodenal damage, do not alter gastric corpus or duodenal prostaglandin generation. Study 5: To define the duodenal physiological parameters that are important in duodenal defense against acid-induced damage, so that the effect of intravenous nicotine on such parameters can be examined in future experiments, we determine the relative importance of duodenal blood flow and duodenal alkaline secretion in the context of acid-induced duodenal injury. We find that enhancement of basal duodenal alkaline secretion is a better predictor of protection against acid-induced deep duodenal damage, than rise in duodenal blood flow. However, the ability to enhance basal duodenal alkaline secretion cannot be the only explanation of the protection against acid-induced damage. Study 6: To prepare for studies of the effect of smoking on human gastrointestinal blood flow, we have completed additional validation experiments for the endoscopic application of the reflectance spectrophotometric technique. The techniques for reproducible demonstration of IHB, ISO_2 and delta ISO_2 (measures of the perfusion status) at the ulcer margin in a dog model, and in patients with active duodenal ulcers have been established.

AWARD # 1KT 94 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Gary J. Schiller, M.D.

INSTITUTION University of California, Los Angeles

TITLE OF PROJECT Stem Cell Transplantation for Small and Non-Small Cell Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Non-small cell lung cancer and small cell cancer of the lung now constitute the leading causes of death due to cancer in California and have been closely associated with the use of cigarettes. In this study we seek to develop a treatment which involves intensive chemotherapy followed by a unique system of blood support, that is the transplantation of circulating blood cells, rather than bone marrow. The purpose in developing this type of blood support is that in many patients with lung cancer, bone marrow is often contaminated with malignant cells and would not be suitable to transplant following high-dose chemotherapy. In this pilot project we investigate the process of obtaining, freezing, and storing cells from the circulating blood for use in transplantation following high-dose chemotherapy. Although we recognize that in the next 30 years effective control of lung cancer will be achieved through reduction of smoking prevalence, there will continue to be a large number of cases of disease. Present chemotherapy for small cell and non-small cell lung cancer produce tumor regression, however, very few patients are long-term survivors. Given the large number of patients with extensive lung cancer for whom surgery is not an option therapeutic strategies must be developed which will have a beneficial impact on causing cancer to regress and increasing survival.

AWARD # RT45 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Stephen D. Wiener, M.D.

INSTITUTION UCLA School of Medicine

TITLE OF PROJECT Retinoic Acid Receptor Expression in Human Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Vitamin A and vitamin A derivatives (retinoids) are critical for maintaining the normal cellular processes of growth and differentiation. Administration of retinoic acid appears to be efficacious in preventing the recurrance of lung cancer and attempts to prevent the development of lung cancer with retinoids are underway. We have been examining the molecular basis for the effects of retinoids on lung cancer by looking at the integrity of three of the retinoic acid receptor genes (α, β, and γ) in lung cancer specimens. Thus far, we have examined more than fifty fresh human lung cancer specimens looking for large scale alteration of several members of the retinoic acid receptor family of genes; we have found alteration of the γ gene pattern in one of the samples. We are uncertain if this represents a normal variant or whether this abnormality can be implicated in the patient's lung cancer. We are now in the process of looking in finer detail at the expression of retinoic acid receptors in this patient and in lung cancer specimens from other patients to determine whether specific abnormalities of the retinoic acid receptor can account for the biological behavior of certain types of lung cancer.

AWARD # 1RT-205-01 AWARD PERIOD 07-01-90 / 06-30-91

PRINCIPAL INVESTIGATOR David Shapiro, Ph.D.

INSTITUTION University of California, Los Angeles

TITLE OF PROJECT Stress & Smoking in Natural Settings: An Ambulatory Study

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The major goal of this project is to evaluate factors affecting the relationship between stress and smoking in everyday life situations using ambulatory recording methods. Observations are currently being made in male and female paramedics during work days and off days. Stress is defined by objective assessments of work- and off-day situations and activities, self-ratings of stress and mood in diaries, and frequent measurements of ambulatory blood pressure and heart rate during the 24-hour observation periods.

Since the actual beginning of the project nine months ago, we have accomplished the following: (1) Research staff were hired, and a postdoctoral fellow is being recruited. (2) Arrangements were made with ambulance services in Fresno and Clovis for participation of paramedics in the research. Responses to subject recruitment have been positive. Arrangements have also been completed to study L.A. County Fire Department dispatchers. (3) Equipment has been purchased, including 4 ambulatory blood pressure recorders (Accutracker II) which have been specially modified for this project. Special instruments have been developed to facilitate the assessment in diaries of smoking behavior, mood, activities, and concomitant consumption of caffeine and alcohol. The use of a palmtop computer has been explored so that subjects can directly record their ratings in the computer. This should greatly increase the efficiency and accuracy of diary information. In conjunction with an engineer, we have designed and are currently completing the development of a device in the form of a cigarette case which will automatically record the date and time each cigarette is taken from the case. (4) A brief summary of experimental results to date follows: 43 subjects (37 males, 6 females) have entered the first study which involves two 24-hour workdays, an off-day, and a lab session. This study is a revised and enlarged version of the first study proposed in the original application. Of these, 11 are smokers. Ten more smokers will be added to complete the study. In the laboratory session, a timed 3-D computerized driving test and a demanding mental arithmetic task are used to simulate some work conditions for purposes of comparison. Analyses of the data are in progress. The data are being organized to permit an examination of relationships between smoking, ambulatory blood pressure and heart rate, different situations during work and off days, stress and mood ratings, periodic ratings by subjects of the urge to smoke and eat, various physical and psychological characteristics of the subjects, other activities, etc. After this study is completed and analyzed, a second study of volunteers from the Fresno community is to be conducted. So far, we have identified 35 smokers interested in participating.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

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Grant Awards by Institution

AWARD # RT 665 AWARD PERIOD 7/1990-6/1993

PRINCIPAL INVESTIGATOR Bungyi Shau

INSTITUTION UCLA School of Medicine

TITLE OF PROJECT Neutrophil cytostatic activity against lung tumor cells

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Tobacco smoking causes significant accumulation of a population of white cells called neutrophils (PMN) in the lung, and depending on the history of smoking, can up or down regulate PMN functions. PMN have been implicated in host resistance to tumor development and their anti-tumor functions have been reported to involve production of a chemical called hydrogen peroxide (HP). The objective of this study is to investigate activation of PMN to develop anti-tumor function with a reagent called tumor necrosis factor, and elucidate the mechanism for regulating PMN anti-tumor function. I have found that TNF-activated PMN can suppress proliferation of various tumor cells including lung tumor cells. This anti-tumor function is dependent on PMN production of HP. Since PMN are in constant contact with red blood cells (RBC) in the blood it is important to investigate RBC effect to understand PMN anti-tumor function in the real human body. I observed that RBC can inhibit TNF-induced PMN anti-tumor activity. Results from the experiments showed that RBC inhibit PMN anti-tumor functions by eliminating the production of HP. RBC have two different mechanisms to eliminate HP. One uses reduced glutathione the other uses catalase. Further studies in this project showed that catalase but not glutathione is responsible for inhibition PMN anti-tumor function. These results suggest that depleting RBC catalase may circumvent their ability to block PMN anti-tumor function and thus, may improve outcome of cancer therapy with TNF.

AWARD # RT 96 AWARD PERIOD 7/90 - 6/91

PRINCIPAL INVESTIGATOR Dennis J. Slamon, M.D., Ph.D.

INSTITUTION UCLA School of Medicine

TITLE OF PROJECT Studies of Proto-oncogenes and Growth Genes in Human Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

In our initial proposal, we proposed to perform the molecular analyses for a number of proto-oncogenes and growth related genes. The significant component of this grant application is the availability of a frozen tumor bank of human non-small cell lung cancer with a large number of the specimens having accompanying normal tissue. In addition, many of the specimens have long term clinical follow-up information. This has allowed us to look for molecular alteration and then attempt correlations with clinical data.

In the past year, we have completed the processing of all samples received in the bank and have begun detailed analyses of the retinoblastoma gene and the p53 gene. To date, we have found that approximately 30% of the samples have Rb alterations and 45% have changes in p53. Correlations with clinical data have shown that Rb alteration was associated with a poorer clinical outcome. In the coming year, we will be looking at additional proto-oncogenes, growth related genes, and tumor suppressor genes.

AWARD # 1 RT-272 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Susan A. Ward, D.Phil.

INSTITUTION UCLA, Department of Anesthesiology

TITLE OF PROJECT Carotid Body Amplification of Exertional Dyspnea in Smokers

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Chronic smoking is associated with shortness-of-breath ("dyspnea") and an impaired ability to exercise. These effects are traditionally thought to arise from smoke-induced stimuli in the airways. I have recently proposed that an additional component may derive from sensors of blood oxygen, carbon dioxide and acidity levels - the "carotid bodies" (CBs) - as smoking causes elevated blood levels of substances that can stimulate the CBs (carbon monoxide, nicotine). This research will therefore determine the role of the CBs in the exertional dyspnea of smokers.

Progress to date includes technical developments (implementation of automated on-line data acquisition and device control by dedicated computer) and studies on nonsmokers (to establish the robustness of techniques and protocols prior to utilizing acute and chronic smoking regimens):

1. Exercise protocol format has been found to exert an important influence on dyspnea. Over a wide range of work rates, subjects experienced greater dyspnea at the same level of breathing during progressive tests compared with constant-load tests imposed in randomized sequences. This likely reflects subjects anticipating the progressive increase in work rate by rating their dyspnea in a similarly progressive fashion. These findings impact significantly not only on the proposed research, but also on the clinical evaluation of dyspnea for which it is common practice to use progressive exercise.
2. Quantification of dyspnea, a subjective variable, could benefit from identification of more objective indices to allow comparisons to be made between subjects. I have evaluated one index - the duration of a volitional breath-hold (BHT) - which has been used at times to quantify respiratory sensation. However, I found that dyspnea and BHT were not uniquely related: while BHT was shorter at higher work rates, it was not proportionally shorter as the pre-BH dyspnea increased (i.e., BHT was considerably longer than expected at high work rates). These results suggest that while the BHT response during exercise coheres qualitatively with that of dyspnea, the relationship is less "tight" than had been predicted.
3. I have also started studies on epinephrine, a CB stimulant. These present a considerable technical challenge, as there are little or no data available on epinephrine dosages during exercise. In response to a controlled intravenous infusion of epinephrine during constant-load heavy exercise, a modest increase in breathing occurred. Dyspnea was also measured in one subject: while dyspnea was greater with the epinephrine infusion, it is not yet clear whether this simply reflects the fact that breathing was increased or whether CB drive was also increased.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

University of California, Riverside

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
4 $1,049,483

b) The subject of research grants by academic discipline:
General Biomedical Science = 3
Pulmonary Disease = 1

c) The relationship between State and Federal funding for tobacco research:
Other State = $23,600
Federal = 0

d) The relationship between each project and the overall strategy of the research program:
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
3 $692,863

g) The number and species of animals used in research:
Hamsters = 300/year
Horses = 25/year
Mice = 135/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
4 $1,049,483

Grant Recipient(s):

1. Eastmond, David A. Gen Biomed
Tobacco smoke, benzene, and mechanisms of leukemogenesis
$224,492 (7/90-6/93)

2. Quinton, Paul Pulmonary
Tobacco smoke and airway fluid transport & composition
$301,620 (7/91-6/94)

3. Talbot, Prudence Gen Biomed
Fertility, smoking, and early mammalian development
$166,751 (7/91-6/93)

4. Ware, Carl F. Gen Biomed
Tobacco product modulation of tnf responses in lung cells
$356,620 (7/91-6/94)

AWARD # 1 KT 36 AWARD PERIOD 7/1/90-6/30/91
PRINCIPAL INVESTIGATOR David A. Eastmond
INSTITUTION University of California, Riverside
TITLE OF PROJECT Tobacco Smoke, Benzene and Mechanisms of Leukemogenesis

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Recent epidemiological studies have found an association between cigarette smoking and the development of leukemia. Benzene, a known leukemia-causing agent in humans, is found in relatively high concentrations in cigarette smoke and is likely to contribute to the increased incidence of leukemia observed in cigarette smokers. The objective of our Tobacco-Related Disease Research project is to investigate the mechanisms involved in benzene-induced leukemia through identifying the types and patterns of chromosomal changes that occur following exposure to benzene and its metabolites. Immunological and molecular biological techniques are being used to study chromosomal changes occuring in 1) isolated human white blood cells exposed to benzene metabolites, 2) the red blood cells of mice exposed to benzene and its metabolites and 3) in the white blood cells of smoking and non-smoking individuals.

Over the past year we have worked to develop and optimize hybridization techniques for the detection of chromosomal changes in human and mouse cells. We are currently applying these techniques to investigate chromosomal changes occurring following the exposure of cells or mice to benzene and its metabolites. Recently, our studies in mice that have shown that a significant percentage (~20%) of the chromosomal changes that occur in the red blood cells following benzene exposure are aneuploid events resulting from the improper segregation of chromosomes in the mouse bone marrow. This establishes the importance of investigating the role of aneuploidy in benzene-induced genotoxicity. These results are complimented by our *in vitro* results using various metabolites of benzene which have demonstrated that exposure of human white blood cells to the benzene metabolite hydroquinone significantly affects cell growth and division resulting in daughter cells containing abnormal numbers of chromosomes. The involvement of various chromosomes in these changes was shown to be non-random. Further investigations are underway to study the mechanisms underlying both aneuploidy-inducing effects as well as chromosome-damaging effects of benzene and its metabolites.

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Source: https://www.industrydocuments.ucsf.edu/docs/mlvl0000

University of California, San Diego

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

36 $7,149,994

b) The subject of research grants by academic discipline:

Cancer	= 6
Cardiovascular Disease	= 2
Epidemiology	= 5
General Biomedical Science	= 13
Public Health, Public Policy, and Economics	= 1
Pulmonary Disease	= 9

c) The relationship between State and Federal funding for tobacco research:

Other State	= $2,865,000
Federal	= $498,141

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

15 $3,161,214

g) The number and species of animals used in research:

Chicks	= 350/year
Dogs	= 20/year
Guinea Pigs	= 40/year
Hamsters	= 60/year
Horses	= 6/year
Mice	= 1,137/year
Monkeys	= 3/year
Rabbits	= 58/year
Rats	= 1,005/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

11 $2,043,262

Grant Recipient(s):

1. Berg, Darwin — Gen Biomed
Nicotine addiction: novel ach receptors on neurons
$369,025 (7/91-6/94)

2. Brown, Joan — Gen Biomed
Nicotinic effects on gene expression in pc-12 cells
$266,647 (7/90-6/93)

3. Burns, David — Epidemiology
Modeling u.S. Lung cancer death rates
$127,276 (7/91-6/92)

4. Conroy, William — Gen Biomed
Neuronal ach receptors: candidates for mediating addiction
$67,344 (7/91-6/93)

5. Criqui, Michael H. — Epidemiology
Smoking, immunoglobulin e, and cardiovascular disease
$49,517 (7/90-6/91)

6. Deng, Tiliang — Gen Biomed
Nicotine-induced changes in gene expression
$70,000 (7/91-6/93)

7. Driscoll, Bryan — Gen Biomed
Probing the nucleotide binding site of protein kinases
$70,000 (7/91-6/93)

8. Foote, Stephen L. — Gen Biomed
Nicotine effects on activity of brain catecholamine neurons
$317,443 (7/90-6/93)

9. Hollenbach, Kathryn — Epidemiology
Relationship between tobacco use and abruptio placentae
$220,007 (7/91-6/94)

10. Howell, Stephen — Cancer
Expression of a drug resistance gene in head and neck cancer
$337,092 (7/91-6/94)

11. Hua, Xiao-Ying — Pulmonary
Release of pulmonary peptides: nicotine & inflammation
$223,588 (7/90-6/93)

12. Kagnoff, Martin — Gen Biomed
Modulatory effects of tobacco products on immune function
$85,627 (7/90-6/91)

13. Kaplan, Robert — Pulmonary
Measurement & outcomes of dyspnea in copd
$291,191 (7/91-6/94)

14. Kelner, Michael J. — Cancer
Preclinical studies of novel agents for lung cancer
$225,000 (7/90-6/93)

15. Klonoff-Cohen, Hillary — Epidemiology
Effects of passive smoking on sudden infant death syndrome
149,416 (7/90-6/92)

16. Klonoff-Cohen, Hillary — Epidemiology
Effects of passive smoking on sudden infant death syndrome
$75,000 (Extension) (7/91-6/92)

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

17. Leffert, Hyam L. Gen Biomed
Benzo[a]pyrene: biogenetic effects on hepatocytes in vitro
$482,971 (7/90-6/93)

18. Liu, Shu Qian Pulmonary
Effects of cigarette smoke on rat pulmonary arteries
$68,650 (7/90-6/92)

19. Mann, Thomas Pulmonary
IL-1 and PDGF: mRNA and protein production by alveolar macro
$69,130 (7/90-6/92)

20. Meinkoth, Judy Gen Biomed
Growth cntrl pathways in thyroid follicular epithelial cells
$225,000 (7/91-6/94)

21. Munafo, Dominic Pulmonary
Leukotriene a4 hydrolase secretion by airway epithelia
$70,000 (7/90-6/92)

22. Nobori, Tsutomu Cancer
Characterization of a new tumor suppressor gene
$200,810 (7/90-6/93)

23. Olman, Michell Cardiovascular
Cigarette smoking alterations in thrombolytic parameters
$70,000 (7/90-6/92)

24. Pierce, John P. Pub Health
Analysis of the effect of natl policies on smoking behavior
$579,489 (7/90-6/93)

25. Pittman, Ray Cardiovascular
Pathways for reverse cholesterol transport
$265,990 (7/90-6/93)

26. Poole, David Pulmonary
Diaphragm structural and metabolic changes in emphysema
$225,000 (7/91-6/94)

27. Rasmussen, Dennis Gen Biomed
A hypothalamic mechanism of nicotine reward and addiction
$62,060 (7/91-6/92)

28. Saatcioglu, Fahri Cancer
Role of jun family of proto-oncogenes in lung cancer
$68,400 (7/90-6/92)

29. Smith, Robert Pulmonary
Smoking-induced alteration of the macrophage nadph oxidase
$76,840 (7/90-6/93)

30. Smith, Robert M. Pulmonary
Smokg-induc mod of resp burst oxidase of human phagocytes
$298,435 (7/90-6/93)

31. Tam, Elizabeth K. Gen Biomed
Human mast cell proteases:func.& exprssn. in smkg-indcd disease
$224,648 (7/90-6/93)

32. Taylor, Palmer Gen Biomed
Nicotinic receptors, tolerance and spinal neurotransmitters
$320,869 (7/91-6/94)

33. Taylor, Susan Cancer
Subcellular localization of camp-dependent protein kinase
$258,345 (7/91-6/94)

34. Vellom, Daniel C. Gen Biomed
Molecular dynamics of acetylcholinesterase mutants
$70,000 (7/90-6/92)

35. Wagner, Peter D. Pulmonary
Determinants of maximum oxygen transport
$282,699 (7/90-6/93)

36. Zanetti, Maurizio Cancer
Vaccine strategy against tumor-associated glycoproteins
$286,485 (7/90-6/93)

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Source: https://www.industrydocuments.ucsf.edu/docs/rmr40068

AWARD # 1RT362 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Joan Heller Brown

INSTITUTION University of California, San Diego

TITLE OF PROJECT Nicotine Effects on Gene Expression in PC-12 Cells

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The physiological effects of nicotine result from the actions of this drug at cellular receptors. These receptors normally respond to the neurotransmitter, acetylcholine. Acetylcholine is released from nerves and rapidly signals muscle cells to contract and gland cells to secrete. Recent data from our lab and others suggests there may also be more chronic or long term responses of cells to acetylcholine. These chronic responses are manifest as changes in cell growth and specific gene expression. The object of our studies is to assess the ability of nicotine to effect gene expression and to compare this to the effect of the stable acetylcholine analog, carbachol. Acetylcholine acts on both muscarinic and nicotinic receptors while nicotine would effect only the latter. We proposed to use PC12 cells but were also interested in using a neuronal cell line, the SK-N-SH cell. These cells are known to have muscarinic cholinergic receptors and a preliminary report suggested that these cells expressed nicotinic receptors. Using SK-N-SH cells we find that carbachol leads to enhanced expression of two immediate early genes, c-fos and c-jun, and of the gene for a putative target protein, the B-amyloid precursor protein. Nicotine has a much more modest effect on expression of c-fos and c-jun message. However, this may be due to the brief duration of stimulation by nicotine. Experiments are in progress to compare the time course of the effects of nicotine and carbachol on c-fos and c-jun expression. We have also carried out experiments examining the involvement of changes in intracellular calcium in the activation of gene expression. Specifically we are characterizing the extent to which increases in intracellular Ca^{++}, as would occur in response to nicotinic and muscarinic receptor stimulation, lead to activation of protein kinase C and a calcium/calmodulin dependent kinase. These are enzymes that catalyze the transfer of phosphate to cellular proteins, and in the case of proteins involved in regulating gene expression, these phosphorylation events may be the primary signals for increasing gene expression.

AWARD # 1RT 180 AWARD PERIOD 07/01/90 to 06/30/91

PRINCIPAL INVESTIGATOR Stephen L. Foote

INSTITUTION University of California, San Diego

TITLE OF PROJECT Nicotine Effects on Activity of Brain Catecholamine Neurons

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Current theories propose that many addictive substances exert their reinforcing effects via actions on brain cells that contain dopamine. These cells are found in regions called the substantia nigra (SN) and the ventral tegmental area (VTA). This proposal will test the hypothesis that doses of nicotine similar to those that accompany cigarette smoking alter the electrophysiological activity of these neurons, specifically by altering the temporal patterning of their discharge activity, and that these pattern changes constitute a substantial component of the addictive actions of this drug.

There is little quantitative information available about the discharge patterns of these dopaminergic neurons and how they are altered by pharmacological manipulations. The development of quantitative assays for these characteristics and the effects of drugs such as nicotine on them is a major goal of this project.

The proposed research will provide a better understanding of the sites and characteristics of nicotine effects on the brain and thus provide essential information on the reinforcing/addictive properties of nicotine.

AWARD # 1RT 468 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Michael H. Criqui, M.D., M.P.H.

INSTITUTION University of California, San Diego

TITLE OF PROJECT Smoking, Immunoglobulin E, and Cardiovascular Disease

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

While the association between smoking and cardiovascular disease (CVD) is well known, the underlying pathophysiological mechanisms are poorly understood. Studies by other investigators have suggested that immunoglobulin E (IgE) mediated events may lead to both platelet aggregation and arterial spasm. Using cross-sectional data, our group has previously shown a positive association between smoking and IgE levels in men, and a weak association in women, and between IgE and total cardiovascular disease in men, but not in women. Although smoking was controlled for statistically in these latter analyses, the data were not stratified on smoking, and all possible definitions of smoking were not evaluated when examining smoking as a potential confounder. New analyses funded by this grant show that the IgE association with CVD remains independent using different definitions of cigarette smoking, and when stratifying by never smokers, ex-smokers, and current smokers.

We accumulated an adequate number of of morbid and mortal events over time in the follow-up of our cohort to evaluate the prospective association of IgE with cardiovascular disease. Exhaustive analyses of the prospective data revealed an overall association for coronary heart disease (CHD) in men, but no association in women. More careful examination of the relationship in men showed that the association between IgE and CHD in men was due to a significant association for only one subcomponent of all coronary disease, non-fatal myocardial infarction. The association for this end point was extremely strong, with a relative risk = 6.6, p-value < .001. In addition, exhaustive analyses of smoking as a confounder, including defining cigarette smoking variously as number of cigarettes per day; past, present, or current smoking; or pack years of smoking, indicated the relationship was completely independent of cigarette smoking. Further stratification of the data by current smokers, ex-smokers, and never-smokers revealed that the relationship was present in all three groups, confirming that smoking was not confounding the relationship. Additional analyses controlling for personal history of allergy of various kinds, and a family history of allergy in parents, siblings, and children, revealed that the IgE association was independent of these variables as well. Finally, the association of IgE was much stronger than the association of any allergic disease with CHD, suggesting that this is primarily an IgE association, rather than any specific allergic association.

AWARD # KT 19 AWARD PERIOD July 1, 1990 - June 30, 1993

PRINCIPAL INVESTIGATOR Xiao-Ying Hua

INSTITUTION Dept. of Anesthesiology, UCSD

TITLE OF PROJECT Release of pulmonary peptides:Nicotine and inflammation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The entire airway, including trachea and lung, is densely innervated by primary C-fibre afferents containing neuropeptides: calchonin gene-related peptide (CGRP), neurokinin A (NKA) and substance P (SP). These peptides exert potent biological activities e.g. they result in vasodilatation, plasma extravasation and bronchial constriction. The present studies are to investigate the effect of various agents known to activate C-fibre terminals on the release of these peptides from the trachea and lung. To investigate this release, novel isolated trachea and lung model have been devised.

Intraluminal perfused rat trachea model Depolarization of the peripheral terminals of primary sensory C-fibre with capsaicin (a specific stimulant of these C-fibres), high concentrations of potassium or electrical field stimulation evoked a significant release of CGRP, NKA and SP from the rat trachea. The release of the peptides was calcium dependent, suggesting a conventional excitation-secretion coupling. Capsaicin demonstrated a concentration-dependent tachyphylaxis with CGRP release. In contrast, prior stimulation with potassium augmented CGRP release induced by a second stimulation with potassium or capsaicin. This suggests a potential "facilitatory" effect of local factors on depolarization evoked release. In fact, several inflammatory substances were examined. Bradykinin induced a direct stimulatory effect on the C-fibre, causing CGRP release, while serotonin and histamine did not cause any release of peptide. Serotonin, however, did significantly enhance CGRP efflux evoked by capsaicin.

Endotracheal perfused guinea-pig lung model Capsaicin and potassium induced release of CGRP and NKA, and simultaneously increased airway pressure. Capsaicin at higher concentration also had pronounced desensitizing effect on both peptide release and airway pressure increase.

In summary, the peripheral terminals of sensory C-fibres in the airway possess releasable stores of three peptides. Such release may create changes in the airway reactivity(oedema and constriction) which are observed in the presence of irritant stimuli.

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AWARD # TRORP 1RT-329 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Martin F. Kagnoff, M.D.

INSTITUTION University of California, San Diego

TITLE OF PROJECT Modulatory Effects of Tobacco Products on Immune Function

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The immune system plays a major role in diseases associated with the use of tobacco (e.g. cancer of the lung and lung infections). Nonetheless, there is little known about the effects of cigarette smoking and other forms of tobacco use on immune function or on the cells, known as lymphocytes, that are important for carrying out immune responses. The major aim of the study was to test the hypothesis that nicotine could significamtly affect the growth and differentiation of lymphocytes important in mediating immune reactions by interactions with a cell surface receptor for nicotine. The studies attempted to demonstrate the presence of receptors for nicotine on B and T lymphocytes, which are the major lymphocyte populations of the immune system. The studies also asked whether nicotine altered the functional properties of B and T lymphocytes.

The functional studies demonstrated that nicotine has no direct effect upon the growth of T or B lymphocytes or on the production of several interleukins and cytokines by T cells. In additional studies, nicotine had no effect on the expression of the IgM, IgG or IgA isotypes by B lymphocytes. In striking contrast, T cells activated by nicotine suppressed the growth of other T cells, when the two populations were mixed. The ability of nicotine to stimulate suppressor activity by T lymphocytes was most striking at high concentrations of nicotine and was reversed by d-tubocurarine. These effects did not appear to be due to the secretion of soluble factors by the nicotine stimulated T cells. Additional studies could not demonstrate the presence of high affinity nicotinic acetylcholine receptors on lymphocytes through receptor ligand binding assays. Studies using Northern blot analysis could not demonstrate expressed mRNA for the α_3 and β_2 chains of the neuronal nicotinic acetylcholine receptor in lymphocytes. Taken together, these studies indicate that lymphocytes respond functionally to nicotine simulation. If such cells express receptors for nicotine, the receptor is either a novel receptor, a low affinity neuronal receptor, a muscle type nicotinic receptor and/or a receptor expressed at a very low level.

AWARD # KT1 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Michael J Kelner

INSTITUTION University of California, San Diego

TITLE OF PROJECT Preclinical studies of novel agents for lung cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Illudins are novel, natural products not currently used for any medicinal purpose. The compounds are found in the Jack O' Lantern mushroom which grows throughout California. Illudins preferentially kill lung cancer cells by a novel mechanism. The tumor cells actively seek to accumulate these compounds inside themselves. Once inside the tumor cells the Illudins are converted to potent toxins. These toxins act by inhibiting the synthesis of DNA which is required for the cancer cell to grow and divide. Normal cells, in contrast, do not actively accumulate the toxins and are not harmed with short exposure times, such as that occurring in an animal. Initial studies demonstrate that certain Illudin analogs can inhibit the growth of lung cancers in animals. These Illudins also stop the spread of these cancer cells to other organs. These lung cancers in animals are not responsive to conventional anti-cancer agents currently available for treating lung cancer. Toxicity studies indicate that Illudins will not harm animals except at doses nearly ten times higher than that needed to treat the lung tumors. Thus, Illudins have a distinct potential advantage over current drugs used to treat lung cancers.

AWARD # KT 38 AWARD PERIOD July 1990 - June 1992

PRINCIPAL INVESTIGATOR Dr. Hillary Klonoff-Cohen

INSTITUTION Dept. of Community & Family Medicine, UCSD

TITLE OF PROJECT Effects of Passive Smoking on Sudden Infant Death Syndrome

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The hypothesis of this study was to determine if infants of either sex who were exposed to passive tobacco smoke and or nicotine exposure through breast milk are more likely to die of sudden infant death than infants who were not exposed. These differences will not be explained by social class, educational levels, or maternal age. The effect of passive smoking on the infant will be examined in women who stopped smoking during pregnancy and then resumed postpartum, as well as in women who never smoked but lived with a smoking partner, thereby exposing the mother during pregnancy and the infant after birth. Preliminary findings at this point in time are two fold. First, there is a large Spanish component in the population that have experienced a SIDS death, contrary to the low rates reported in the literature. Second, mobility for the SIDS parents is extremely high in Southern California and requires complex tracking procedures. Based on the interviewed families thus far, the preliminary trend seems to bear out the hypothesis of a relationship between passive smoking and SIDS.

AWARD # 1RT-137 AWARD PERIOD July 1, 1990-June 30, 1991

PRINCIPAL INVESTIGATOR M.L. Leffert

INSTITUTION UCSD

TITLE OF PROJECT Benzo(a)pyrene Biogenetic Effects of Heparocytes In Vitro

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

We are trying to determine how benzo[a]pyrene, the principal chemical carcinogen contained in cigarette smoke, might cause liver cancer. To investigate this problem, we are studying the effects of benzo[a]pyrene directly on the growth and differentiation of normal rat hepatocytes in primary tissue culture.

In particular, we are examining 1) the mechanism(s) by which carcinogen-DNA adducts (sites on DNA molecules to which benzo[a]pyrene binds co-valently) alter hepatocyte gene expression; and, 2) whether or not the presence of one or more "oncogenes" inside hepatocytes alters growth control or sensitizes the cells to chemical transformation by benzo[a]pyrene.

Preliminary findings suggest that gene expression is altered when carcinogen adducts are situated randomly along DNA molecules. In our model system, a single adduction site per supercoiled molecule of plasmid DNA appears to be sufficient to abolish reporter gene expression in hepatocytes transfected with such DNA. Thus far, the available data indicate that this "site" need not be present either in the reporter gene itself or in the promoter region which regulates the gene. If it is correct, this observation could have a significant impact on theories of chemical carcinogenesis.

Initial findings with hepatocytes transfected with plasmids expressing either reporter genes or proto-oncogenes driven by strong promoters suggest complex interactions between endogenous cellular and inserted plasmid promoters. These observations are significant technically, since these experiments can ofter lead to artifacts or misinterpretation of results unless chimeric DNA interactions are understood precisely.

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2023471131

Award# IFT 64 Award Period July 1990 – July 1992

Principal Investigator Shu Qian Liu

Institution University of California, San Diego

Title of Project Effects of cigarette smoke on rat pulmonary arteries.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Effects of cigarette smoke on the mechanical properties of the pulmonary arteries are studied in 8 smoking and 8 control rats. A smoking machine, in which the smoke density, puffing duration and frequency, and cigarette butt length are well controlled according to that in human smokers, is used in the study. After 2 (4 rats) and 3 months (4 rats) smoking with 14 cigarettes each day, the rats are sacrificed and the zero-stress states and mechanical properties of the pulmonary arteries are investigated. The zero-stress states of the pulmonary arteries are obtained by first cutting the vessel transversely into a series of short ring-shaped segments, and then cutting each ring radially. The arterial ring opens into a sector immediately. The opening angle of the sector is measured to describe the zero-stress state. The mechanical properties of the arteries with outer diameter about 400 μm are determined by the pressure–diameter, and –length relationship, and pipette aspiration *in vitro*. The pressure–diameter, and –length relationship is obtained in the pressure range of 0 to 30 mm Hg. After the determination of the pressure–diameter, and –length relationship, two micropipettes with rectangular mouth (100x1,000 μm) are applied symmetrically to the same artery with the length of the mouth aligned to the central line of the vessel in the longitudinal direction. The aspirated distance of the pulmonary arteries in the pipette is determined. Specimens of the pulmonary arteries are also collected for histological study.

The opening angles of the pulmonary arteries did not change in the 2 month smoking rats, but increased significantly in the small arteries in the 3 month smoking rats comparing with the corresponding controls, respectively. The extensibility of the pulmonary arteries in both circumferential and longitudinal directions decreased significantly in 2 and 3 month smoking rats. The pipette aspiration test showed that the aspirated distance of the pulmonary arteries into the pipette decreased greatly in the 2 and 3 month smoking rats comparing with that of the controls. Data from both pressure–diameter and –length relationship and pipette aspiration show that the compliance of the pulmonary arteries decreases in smoking rats. There are no obvious differences between 2 and 3 month smoking rats in the vessel compliance. Increase of collagen density in the adventitia of the pulmonary arteries was found in histological sections. Black spots were found under the surface and in the parenchyma of the lungs in both 2 and 3 month smoking rats, but not in the controls. Histological examination showed that smoke particles and crystalline-like structures were included in the black spots.

AWARD # IFT-55 AWARD PERIOD 1990-91

PRINCIPAL INVESTIGATOR Thomas Mann, M.D.

INSTITUTION University of California, San Diego

TITLE OF PROJECT IL-1 and PDGF: MRNA and Protein Production by Alveolar Macro

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Most destructive processes of the lung are mediated through a variety of inflammatory processes. We have obtained some insight as to the mechanism(s) of destruction in processes such as adult respiratory lung disease and idiopathic pulmonary fibrosis. In contrast, an understanding of the process leading to the destruction of lung tissue characterizing emphysema remains largely unknown. In recent years a host of potent inflammatory molecules made by the body have been described. Additionally, powerful molecular biologic methods such as polymerase chain reaction (PCR) and immunohistochemistry have been developed to investigate the regulation and production of these factors. Using these techniques, we are studying the production of two such inflammatory mediators (interleukin-1 or IL-1 and platelet-derived growth factor or PDGF) by the alveolar macrophage in smokers and non-smokers.

To date, we have examined the alveolar macrophages of eight non-smokers for the presence of TNF mRNA. As expected, this message was not found in any of these patients. Additionally, we have studied the alveolar macrophages from patients undergoing thromboendarterctomy (an excellent clinical model of acute pulmonary inflammation) and seen the production of TNF mRNA following this procedure. We have developed important positive controls for mRNA to IL-1α, IL-β, PDGF-α, PDGF-β, tumor necrosis factor (TNF) and interleukin-8 using a stimulated macrophage-like cell line, THP$_1$. Additionally, a working standard control for β-actin has been established. Finally, we have worked on quantifying the number of cytokine transcripts using PCR. These efforts are detailed in the technical section. In the coming year we plan to continue our investigation of clinical material based on the expertise we have developed during the past year.

AWARD # IFT 22 AWARD PERIOD 1990-91

PRINCIPAL INVESTIGATOR Dominic A. Munafo M.D.

INSTITUTION University of California, San Diego

TITLE OF PROJECT Leukotriene A_4 Hydrolase Secretion by Airway Epithelia

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

I have been studying the role that leukotrienes play in airway disease. Leukotrienes are a family of fatty compounds derived from components of cellular membranes. These fats are some of the most potent natural mediators of inflammation yet found. They affect inflammatory cell migration, adherence and activation as well as influencing the permeability of blood vessels and the muscular tone of blood vessels and airways. The fat leukotriene A_4 (LTA_4), is the crucial intermediate from which all other leukotrienes are synthesized. It can be converted by an enzyme (LTA_4 hydrolase), to another fat named LTB_4. LTB_4 has been shown to be one of the most potent attractors of inflammatory cells known. The effects of LTB_4 on airway function include airway constriction, recruitment of inflammatory cells to the airway, and stimulation of inflammatory cells to adhere and secrete a variety of pro-inflammatory products. We have previously demonstrated that human airway lining cells contain the enzyme which converts LTA_4 to LTB_4.

The principal hypothesis of my tobacco grant is that secretion of this enzyme by the airway lining cells plays a role in the development of airway diseases. The specific aim of the proposal is to confirm our preliminary observations that the enzyme is secreted by human airway lining cells. In an attempt to further define the role of the enzyme in lung inflammation I began assaying human lung lining fluid for its presence. I found that lung lining fluid did contain the enzyme and that it was active. The results of this work were formally presented at the American Federation of Clinical Research meeting in May 1991, in Seattle, Washington.

In the ensuing months I hope to further explore the presence of this enzyme in lung lining fluid as well as further characterize its possible secretion by airway lining cells. Furthermore, we will explore ways to modulate its secretion. The potential to modulate these mediators of airway inflammation may prove crucial to the development of effective therapy in tobacco-related lung disease.

AWARD # 1KT112 AWARD PERIOD 07/01/90-06/30/91

PRINCIPAL INVESTIGATOR Tsutomu Nobori, M.D.

INSTITUTION University of California, San Diego

TITLE OF PROJECT Characterization of a new tumor suppressor gene

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cigarette smoking increases the frequency of cancers arising from the lung, bladder, esophagus and stomach. Although genetic events that lead to cancer are not known precisely, alterations in cellular oncogenes are thought to play a critical role in tumorigenesis. Dominant oncogenes, however, are unable to explain such findings as (1) reversion by the fusion of the tumor cells with the normal cells and (2) chromosomal deletions frequently seen in human cancers. Chromosomal deletions and/or loss of a specific chromosomal locus suggest that a tumor suppressor gene important in the genesis of that tumor may be present within the missing chromosomal locus. A sensitive method of identifying loss of chromosomal loci in tumors involves the use of the DNA markers that detect restriction fragment length polymorphisms (RFLPs). Loss of heterozygosity or allelic loss in tumor DNA indicates that tumor cells have lost one allele at the chromosomal locus identified by the DNA marker. Moreover, by analogy with esterase D deficiency in retinoblastoma, the enzyme deficiency may signal the presence of the tumor suppressor genes. The enzyme methylthioadenosine phosphorylase (MTA phosphorylase), the gene (MTAP) for which has been mapped to the short arm (designated p) of human chromosome 9, is deficient in a number of different malignant cell lines, although all lines derived from normal cells contain abundant levels of the enzyme. Cytogenetic analysis showed that many leukemias, glioblastomas, lung cancers, bladder carcinomas and melanomas had deletions or translocations affecting the 9p region and chromosome 9 monosomy. The objectives of this research are to measure the enzyme activities in human cancers and to determine the causes and consequences of MTA phosphorylase deficiency, and the accompanying chromosomal loss of loci for chromosome 9p in malignancy. We have employed the radiochemical enzyme assay and the immunoblotting procedure to screen human solid tumors including gliomas, melanomas, lung cancers, and bladder carcinomas. MTA phosphorylase deficiency was found in 10 (5 cell lines and 5 primary tumors) of 14 gliomas (8 cell lines and 6 primary tumors), 1 of 10 melanomas, 2 of 8 lung cancers, and 2 of 10 bladder carcinomas. We then carried out genetic analysis of 9 glioma cell lines. None of 5 cell lines lacking MTA phosphorylase activity contained the complete interferon-α (IFNA) gene cluster. Three of them were found to have two copies of the interferon-β1 (IFNB) gene. Partial or complete deletion of the IFNA gene cluster was well correlated with MTA phosphorylase deficiency. Taken together, these data suggest (i) that the interferon genes are not likely to be the real tumor suppressor genes, (ii) that the MTAP locus is more closely linked to the IFNA gene cluster than the IFNB gene and other chromosome 9p-associated genes analyzed in these studies, and (iii) that the MTAP locus is more closely linked to putative tumor suppressor genes than the IFNA gene cluster.

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AWARD # 1FT 66 AWARD PERIOD 1990-91

PRINCIPAL INVESTIGATOR Mitchell Olman

INSTITUTION University of California, San Diego

TITLE OF PROJECT Cigarette Smoking alterations in Thrombolytic Parameters.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

There is a generally accepted association between cigarette smoking and the formation of thrombi in blood vessels. Depending on location, thrombi can lead to diseases associated with significant morbidity and mortality including myocardial infarction, cerebrovascular accidents and pulmonary embolism. UCSD Medial Center is an international referral center for one such disease know as chronic thromboembolic pulmonary hypertension. The goal of this study is to define the possible causal role of cigarette smoking to this disease. To this ead, we measured the blood levels of various components of the blood that are involved in the dissolution of thrombi and compared the smokers and non-smokers in the patient group and in normal volunteers. As compared with normals, the patients with pulmonary thrombi have an increased level of the blood enzyme involved in thrombus dissolution in response to a simulated venous thrombus gencrated by transient blood pressure cuff inflation. The response was similar in nonsmokers, ex-smokers or current smokers. We are continuing to study the biochemical behavior of the blood cells which line the blood vessels (endothelial cells) obtained from these patients.

AWARD # 1RT 245 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR John P. Pierce

INSTITUTION University of California, San Diego

TITLE OF PROJECT Analysis of the Effect of National Policies on Smoking Behavior

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Data on smoking behavior in the United States has been collected for over 30 years. We know that smoking data varies considerably by birth cohort as well as by age. The birth cohort differences probably relate to the knowledge of health consequence and to specific interventions that took place at different times over the past 30 years. We have combined data from the NHIS population based surveys spanning a period of nearly 25 years to ensure adequate sample size for analyses within and across birth cohorts of the population. Within these birth cohorts we will be able to undertake subgroup analyses of smoking variables across time by race, gender and educational level.

In describing smoking for a particular birth cohort the variables of major interest are the rate and timing of initiation, the overall peak prevalence of smoking attained and the rate and timing of cessation. The first set of analyses that we have undertaken on the combined data set generated profiles of the age of smoking initiation by birth cohort. In the earlier birth cohorts white women have a much wider distribution for age of initiation than white men. These differences are less with each successive birth cohort. Similar differences are observed for black men compared to white men.

The smoking curves for each birth cohort have been generated. There is a clear birth cohort effect on the peak prevalence attained across each subgroup. Within a birth cohort, the current smoking prevalence curves differ markedly for the race-gender subgroups. Also, early plots of the rate of cessation suggest that the effect of time and events on cessation has changed markedly over the last thirty years for each of the different race-gender-education subgroups. We have collected information with which to link events with time (from Readers Guide) and will proceed to correlate these with behavior after we have completed the more definitive analysis.

The early data from this project justify our feeling that this type of analysis would lead to many new insights into what has worked and what has not in smoking interventions over the last thirty years.

AWARD # RT 399 AWARD PERIOD 2/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Ray Pittman

INSTITUTION University of California, San Diego

TITLE OF PROJECT Pathways for Reverse Cholesterol Transport

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Smokers face an excess risk of coronary artery disease. HDL cholesterol levels are inversely related to the incidence of coronary artery disease, and smoking decreases HDL cholesterol and apoprotein levels. The decreased HDL may account substantially for increased cardiovascular risk in smokers. This does not mean that increasing HDL levels by any means will necessarily reduce risk, and the role of HDL must be understood. That is the focus of this proposal. The most widely accepted mechanism for the beneficial role of HDL invokes its involvement in the return of cholesterol from extrahepatic tissues to the liver for excretion or reutilization (reverse cholesterol transport). Several pathways may participate in this, but we do not know what roles they actually play in vivo. We are seeking to determine that in this grant. One hypothesis to be tested is that a novel pathway for the direct cellular uptake of HDL cholesterol esters ("selective uptake"), which we have described, plays a role in reverse cholesterol transport in humans. Rabbits represent an extreme test of the hypothesis since they are less likely than humans to express selective uptake. Our early studies used a kinetic modelling approach to demonstrate selective uptake even in rabbits. No matter what the extent of the pathway in humans, it may play a protective role which should be amplified. ¶To eventually measure selective uptake in humans, we are developing a more direct and simpler methodology that will give clearer answers more easily. This requires a tracer of cholesterol esters (CE) which behaves just as endogenous CE esters except that it is not transferred between lipoprotein particles in vivo by a CE transfer protein present in the plasma of rabbits and humans. We have now studied in rabbits several tracers which meet these criteria to varying degrees, and in the process have verified the presence of selective uptake in rabbits. However, transfer between lipoproteins was greater than predicted from studies in vitro. Other tracers are now being explored. ¶While developing methodology, we have also carried out studies on the effect of probucol on reverse cholesterol transport. This drug lowers HDL levels but nevertheless has apparent anti-atherosclerotic activity. Probucol treatment of rats lowered HDL levels by >30%, but did not diminish the transport of CE to the liver in HDL at all. This maintenance of near normal reverse cholesterol transport was due to induction of selective uptake in the liver; parallel results were seen in a human liver cell line. Induction of hepatic selective uptake by probucol may serve as a model for other drugs useful in smokers and others at atherosclerotic risk.

AWARD # FT 6 AWARD PERIOD July 1, 1990 - June 31, 1992

PRINCIPAL INVESTIGATOR Fahri Saatcioglu, Ph.D.

INSTITUTION University of California, San Diego

TITLE OF PROJECT The Role of Jun Family of Proto-oncogenes in Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Lung cancer is the leading cause of cancer deaths in the U.S. and Europe. Approximately 90% of lung cancer deaths and almost one third of the deaths from cancer of all kinds can be traced directly to smoking. While prevention strategies aimed at cessation of smoking are necessary, dramatically more sensitive diagnostic assays and effective therapies are urgently needed for the large number of people developing lung cancer each year. These have to be based on a better understanding of the events in the carcinogenesis of the lung at the molecular biological level of the cell. To that end, we have begun to investigate the modulation of the AP-1 transcriptional activating complex, composed of c-Jun and c-Fos oncoproteins, which is at a central position in the regulation of cell growth and proliferation and in the oncogenic process. With respect to lung cancer, it is important to realize that AP-1 activity, c-jun and c-fos gene expression, are stimulated by exposure to tumor promoters and carcinogens which are abundant in tobacco smoke and also by the ras and raf oncogenes which are implicated in many different types of lung cancer. AP-1 is also negatively regulated by retinoic acid, an agent which decreases susceptibility to lung cancer. Therefore it appears that modulation of AP-1 activity occupies a central role in the etiology of this neoplastic disease.

We have begun to investigate the mechanisms by which retinoic acid and other antitumor promoters may function by inhibiting the AP-1 complex. Building on the recent findings that the retinoic acid and the glucocorticoid receptors when bound to their ligands can suppress AP-1 activity in vivo, we have started to characterize the details of this phenomenon. We found that the thyroid hormone receptor (TR), another member of the same receptor superfamily, can also interfere with AP-1 activity in vivo. This is of interest since many small cell tumors of the lung carry a deletion on chromosome 3 which may overlap with one of the TR genes. While TRα (c-erbA) efficiently blocked AP-1 activity in HeLa and CV1 cells, the viral homologue v-erbA was not able to do so. Chimeras between c-erbA and v-erbA were constructed and tested for their ability to interfere with AP-1 activity to locate the region most important in the interaction of c-erbA and AP-1. We found that a 9 amino acid segment at the carboxy terminus of c-erbA which is deleted in v-erbA is the main mediator of the interaction between c-erbA and the AP-1 complex. When a similar region at the analogous position in the retinoic acid receptor was deleted, it also lost its ability to interfere with AP-1 activity. This region was also found to be important for the ability of both the thyroid and retinoic acid receptors to transactivate from their response elements. The mutant receptors deleted in this regions interfered with the ability of the wild-type receptors to either block AP-1 activity or to activate transcription. These results provide some of the details of the molecular events which may be involved in carcinogenesis of the lung and thereby may lead to the development of diagnostic and therapeutic tools for this disease

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AWARD # 1KT32 AWARD PERIOD 7/1/90-6/30/92

PRINCIPAL INVESTIGATOR Robert M. Smith, M.D.

INSTITUTION University of California, San Diego Medical Center

TITLE OF PROJECT Smoking-Induced Alteration of the Macrophage NADPH Oxidase

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Free radicals are highly reactive molecules which have been implicated in a number of tobacco-related diseases including pulmonary emphysema, atherosclerosis, carcinoma, and pulmonary fibrosis. Tobacco smoke contains free radicals but the short life span of these substances make it unlikely they act directly to cause most smoking related diseases. Alternatively, tobacco products may act indirectly by inducing the body's phagocytic cells [circulating blood neutrophils and monocytes, and lung and tissue macrophages] to produce large quantities of oxygen-derived radicals. The focus of this project is to understand the NADPH oxidase, the multi-component enzyme system used by phagocytes to produce oxygen-derived radicals, and to examine the effect that tobacco products may have on the activity of the system. All of the components of this enzyme system have not been previously identified and so the understanding of its regulatory mechanisms is incomplete. Efforts over the past year have successfully focused on identifying the remaining components of the NADPH oxidase and developing assays of sufficient sensitivity and specificity for the known components. Studies supported by this grant have identified a 31 kDa NADPH-binding protein which is believed to contain the catalytic center of the enzyme system. Work is continuing on methods to purify enough of this novel oxidase component to allow amino acid sequencing and subsequent isolation of the encoding cDNA. In additional experiments, antibodies have been raised against peptides specific to the previously identified components of the oxidase. These antibodies are currently being used to develop assays to look at the effect of smoking on oxidase levels and function. Preliminary studies suggest that the intracellular location of these components within the phagocytic cell correlates with oxygen radical production of the cell. If confirmed, examination of cells from smokers will allow prediction of the activity of the oxidase in vivo.

AWARD # 1RT 457 AWARD PERIOD 7/1/90-6/30/92

PRINCIPAL INVESTIGATOR Robert M. Smith, M.D.

INSTITUTION University of California, San Diego Medical Center

TITLE OF PROJECT Smoking-Induced Modification of the Respiratory Burst Oxidase of Human Phagocytes

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Free radicals are highly reactive molecules which have been implicated in a number of tobacco-related diseases including pulmonary emphysema, atherosclerosis, carcinoma, and pulmonary fibrosis. Tobacco smoke contains free radicals but the short life span of these substances make it unlikely they act directly to cause most smoking related diseases. Alternatively, tobacco products may act indirectly by inducing the body's phagocytic cells [circulating blood neutrophils and monocytes, and lung and tissue macrophages] to produce large quantities of oxygen-derived radicals. The focus of this project is to understand the NADPH oxidase, the multi-component enzyme system used by phagocytes to produce oxygen-derived radicals, and to examine the effect that tobacco products may have on the activity of the system. All of the components of this enzyme system have not been previously identified and so the understanding of its regulatory mechanisms is incomplete. Efforts over the past year have successfully focused on identifying the remaining components of the NADPH oxidase and developing assays of sufficient sensitivity and specificity for the known components. Studies supported by this grant have identified a 31 kDa NADPH-binding protein which is believed to contain the catalytic center of the enzyme system. Work is continuing on methods to purify enough of this novel oxidase component to allow amino acid sequencing and subsequent isolation of the encoding cDNA. In additional experiments, antibodies have been raised against peptides specific to the previously identified components of the oxidase. These antibodies are currently being used to develop assays to look at the effect of smoking on oxidase levels and function. Preliminary studies suggest that the intracellular location of these components within the phagocytic cell correlates with oxygen radical production of the cell. If confirmed, examination of cells from smokers will allow prediction of the activity of the oxidase in vivo.

AWARD # KT 53 AWARD PERIOD July 1, 1990 - June 30, 1992

PRINCIPAL INVESTIGATOR Elizabeth K. Tam

INSTITUTION San Diego VA Medical Center/UC San Diego

TITLE OF PROJECT Human Mast Cell Proteases: Function & Expression in Smoking-Induced Disease

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Mast cells are specialized cells which reside in many tissues. In the human lung they are particularly abundant in the connective tissue of nerves, blood vessels, and alveoli (the actual units where the exchange of gases occurs). In these microenvironments, they can release chemicals that directly or indirectly change cell or tissue function. This research focuses on how mast cell-derived proteases -- enzymes which break chemical bonds in proteins -- may contribute to the connective tissue destruction of emphysema or to the inflammation seen in chronic bronchitis. We have now isolated 2 proteases from human lung. One is confirmed to be mast cell tryptase, and the other is a novel protease which may or may not be derived from mast cells, but is very similar to the mast cell "chymase." We are currently characterizing this second protease more fully, by determining the sequence of amino acids of which it is made, its preference for particular synthetic substrates, and its inhibition by protease inhibitors. Once we have more fully characterized this second protease and the cell which synthesizes it, we will determine whether each of these purified proteases cleaves proteins which make up the connective tissue of human lung or whether they cause the release of inflammatory products from endothelial cells, which line the inside of blood vessels feeding the lung and airway. To lay the foundation for the latter work, we have already devised successful techniques to isolate endothelial cells from human pulmonary artery, maintain them in pure culture, and assay arachidonic acid products released in their response to well known stimulatory agents. Finally, to determine the likelihood of these interactions occurring naturally in the lung, we will study the distribution of the proteases in relation to connective tissue or blood vessel constituents in the human lung. Tissue sections from more than 15 smokers and non-smokers have already been collected and prepared for special staining to detect the proteases.

AWARD # FT 43 AWARD PERIOD 11/1/1990 thru 6/30/1991

PRINCIPAL INVESTIGATOR Daniel C. Vellom, Ph.D.

INSTITUTION U. C. San Diego, Department of Pharmacology

TITLE OF PROJECT Molecular Dynamics of Acetylcholinesterase Mutants

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Nicotine acts through a family of neurotransmitter receptors in the central and peripheral nervous systems to exert its pharmacological actions and longer term deleterious effects. The natural neurotransmitter for the nicotinic receptor system is acetylcholine, and the hydrolytic enzyme acetylcholinesterase (AChE) is responsible for rapid turnover of acetylcholine in the cholinergic synapse. Although the genes for the nicotinic receptors and for several acetylcholinesterases have been cloned, less knowledge is available on the influence of higher order structure on catalytic function. The objective of this research is to examine the role of membrane anchoring on the molecular dynamics of acetylcholinesterase. We wish to generate several forms of acetylcholinesterase with various membrane anchoring functions and quaternary structures in order to assess their effects on the activity and segmental flexibility of the protein.

The hydrophobic form of Torpedo acetylcholinesterase is anchored to the cell membrane by a glycophospholipid and exists as a dimer of identical catalytic subunits. Other proteins such as the epidermal growth factor receptor are anchored to the cell membrane by a transmembrane peptide. In order to assess the effects of these two different anchoring motifs on the activity and molecular dynamics of mammalian acetylcholinesterase, we have used recombinant DNA techniques to generate novel DNA's which will direct the synthesis of mouse AChE's with these different anchoring functions. The technique of oligonucleotide directed mutagenesis was used to create unique restriction enzyme cleavage sites in the cloned DNA's coding for mouse AChE, Torpedo hydrophobic AChE, and human EGF receptor. These sites were then used to splice specific DNA fragments together, creating the new chimeric genes. In addition, a further round of mutagenesis was used to produce a chimeric DNA which codes for a monomeric form of hydrophobic mouse AChE. The integrity of the newly created sequences was verified by DNA sequencing. The chimeric DNA sequences were then cloned into plasmid vectors which will allow expression in cultured cells. Fluorescent and phosphorescent chemical probes which are specific for the active site of acetylcholinesterases will be used to label the expressed proteins either in situ or after purification. The molecular dynamics of these labeled proteins may then be measured spectroscopically and compared to the native forms.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # 1RT 227 AWARD PERIOD July 1, 1990 - June 30, 1993

PRINCIPAL INVESTIGATOR Peter D. Wagner, M.D.

INSTITUTION University of California San Diego

TITLE OF PROJECT DETERMINANTS OF MAXIMUM OXYGEN TRANSPORT

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Considerable uncertainty remains regarding the factors that determine the maximum rate of utilization of oxygen by the body during maximal exercise. We have advanced a quantitative theory that predicts maximum oxygen utilization on the basis of oxygen transport between the air and the muscle cells. This transport is broken down into two major components, based upon convective and upon diffusive modes of movement of oxygen through the system. The research proposal seeks to obtain evidence to support or refute this hypothesis, and if supported, to use it to better understand the relative importance of specific parts of the pathway for oxygen diffusion between the red cell in the blood capillary of the muscle and the final site of oxygen utilization in the muscle cell, the mitochondrion. A number of studies have been completed and others are in progress under the tenure of this award. First, we have now shown that the level of hemoglobin concentration in the blood plays an important role in the diffusion of oxygen out of the blood, accounting for approximately half of the diffusion resistance. Future questions will address how this occurs. Another project has examined how a change in oxygen binding to hemoglobin affects oxygen diffusion, showing that when binding between oxygen and hemoglobin is tight, maximum oxygen uptake is reduced predictably. In a third project, we examined the relationships between the supply of oxygen to muscle cells, and the subsequent biochemical usage of oxygen in an *effort* to understand the linkage between the physiological and biochemical manifestations of maximum exercise. The results are consistent with oxygen availability limiting the speed at which biochemical reactions run during maximal exercise. Work in progress has demonstrated in normal humans that when the entire body is at maximum VO_2, so too are the muscles producing that maximum exercise (a subtle but never before demonstrated observation). Finally, work in progress shows that breathing of pure oxygen increases maximum VO_2 in proportion to the enhancement of delivery of oxygen in the blood to the muscles.

AWARD # RT 70 AWARD PERIOD July 1, 1990 - June 30, 1992

PRINCIPAL INVESTIGATOR Maurizio Zanetti, M.D.

INSTITUTION University of California San Diego

TITLE OF PROJECT Vaccine Strategy against tumor-associated Glycoproteins

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The approach proposed is based on the hypothesis that antibodies can mimic the function of a tumor-associated antigen and can, therefore, be used to generate active anti-tumor immunity. As a tumor-associated antigen we work on the Thomsen and Friedenreich or T and Tn antigens expressed in ~90% of lung cancer of various histological type. We will experimentally verify that antibodies appropriately selected to mimic T and Tn antigens produce the desired effect and induce a protective and specific tumor immune response.

Experiments will be conducted to generate a large number of monoclonal antibodies that will be tested in vitro and in vivo for their ability to substitute for the tumor-associated antigen. We will ascertain the ability of the chosen antibody(ies) to induced either humoral or cellular immunity, or both. The work will be guided by the use of an animal model that resembles in many respects to human carcinoma.

This study may allow us to identify a new way to induce protective immunity against cancer translatable into treatment and prevention human lung cancer. The ultimate goal of the approach under study is identify an antibody that holds promise for human vaccination and protection from tumor development and/or progression.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

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Grant Awards by Institution

University of California, San Francisco

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

53 $16,910,401

b) The subject of research grants by academic discipline:

Cancer	= 4
Cardiovascular Disease	= 8
Epidemiology	= 6
General Biomedical Science	= 11
Public Health, Public Policy, and Economics	= 11
Pulmonary Disease	= 6
Tobacco-Use Prevention, Intervention, and Cessation	= 7

c) The relationship between State and Federal funding for tobacco research:

Other State	= $563,837
Federal	= $2,002,731

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

8 $2,129,180

g) The number and species of animals used in research::

Pigs	= 47/year
Rabbits	= 170/year
Rats	= 840/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

5 $1,818,506

Grant Recipient(s):

1. Adler, Nancy E. Intervention
Pregnant smokers: predictors of cessation and relapse
$453,944 (7/90-6/93)

2. Baker, David Pulmonary
The effect of cigarette smoke on airway neuronal receptors
$225,260 (7/91-6/94)

3. Baluk, Peter Gen Biomed
Effects of cigarette smoke on nerve and blood vessel growth
$224,357 (7/91-6/94)

4. Barker, Judith Pub Health
Ethnicity and the meaning of smoking in older age groups
$317,076 (7/91-6/93)

5. Basbaum, Carol Pulmonary
The effects of tobacco smoke on airway mucin mRNA
$71,867 (7/91-6/92)

6. Bero, Lisa Pub Health
The tobacco industry and scientific research
$220,709 (7/91-6/94)

7. Blanc, Paul Epidemiology
Effects of cigarette smoking in low-dose zinc fume inhalation
$225,000 (7/91-6/94)

8. Burlingame, A. Pulmonary
Smoke-induced differential expression of cellular proteins
$257,010 (7/91-6/94)

9. Cashman, John Gen Biomed
Human markers for(s)-nicotine biotransformation & pathology
$58,898 (7/91-6/92)

10. Cason, Brian A. Cardiovascular
Oxygen effects on flow & function in ischemic myocardium
$278,044 (7/90-6/93)

11. Cohen, Robert Cancer
Molecular basis of lung cancer metastasis
$223,993 (7/91-6/94)

12. Cooper, Douglas Pulmonary
Function in lung matrix of a laminin-binding lectin
$225,000 (7/91-6/94)

13. Coughlin, Shaun Cardiovascular
Determinants of thrombin interaction with its receptor
$244,243 (7/91-6/94)

14. Croughan-Minihane, Mary Intervention
Smoking intervention for women seen in primary care practice
$218,178 (7/90-6/93)

15. Cummings, Stephen Intervention
Do follow-up visits help patients quit smoking?
$745,189 (7/91-6/94)

16. Curtis, Donald Gen Biomed
Stabilizing the occlusion in the dentate hemimandibulectomy
$104,037 (7/91-6/93)

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Source: https://www.industrydocumentslibrary.ucsf.edu/tobacco/

17. Dodson, Barbara — Gen Biomed
Effects of sedatives on neuronal nicotinic binding
$394,301 (7/90-6/93)

18. Erle, David J. — Gen Biomed
Effects of cigarette smoking on leukocyte adhesion molecules
$223,015 (7/90-6/93)

19. Ernster, Virginia L. — Epidemiology
Cigarette smoking and facial wrinkling
$528,147 (7/90-6/93)

20. Finkbeiner, Walter E. — Pulmonary
In vitro characterization of human airway gland cells
$511,793 (7/90-6/93)

21. Franzgrote, Merula — Intervention
Assessment of teen tobacco use by primary care physicians
$70,000 (7/91-6/93)

22. Gibson, Bradford — Cancer
Phosphoryl peptide inhibitors of tyrosine kinases
$308,697 (7/91-6/94)

23. Glantz, Stanton A. — Pub Health
Tobacco industry response to passive smoking
$484,233 (7/90-6/93)

24. Hardman, David — Cardiovascular
Smoking and lipoprotein-based mechanisms of atherogenesis
$70,000 (7/90-6/92)

25. Hellerstein, MarcPub Health
Substrate cycles, calorigenesis and smoking cessation
$378,709 (7/90-6/93)

26. Ishii, Kenji — Cardiovascular
Mechanisms of thrombin/receptor interaction
$69,175 (7/91-6/93)

27. Jacob, Peyton — Pub Health
Clinical pharmacology of tobacco alkaloids
$538,143 (7/90-6/93)

28. Kane, John — Cardiovascular
Effects of smoking on high density lipoprotein species
$203,942 (7/90-6/93)

29. Kane, John — Cardiovascular
Smoking and lipoprotein-based mechanisms of atherogenesis
$250,645 (7/91-6/94)

30. Kramer, Randall — Cancer
Oral cancer: adhesive interactions during progression
$309,025 (7/91-6/94)

31. Kaur, Surinder — Gen Biomed
MS studies of tobacco — specific adducts with hemoglobin
$225,000 (7/90-6/93)

32. Lee, Philip R. — Pub Health
Prop 99 & indigent care:lessons for future health care reform
$589,893 (7/90-6/93)

33. Leffler, Hakon — Pulmonary
An endogenous lectin in airway epithelium and lung cancer
$463,703 (7/90-6/93)

34. Levine, Jon — Gen Biomed
Nicotine enhanced adrenal medullary-dependent inflammation
$363,563 (7/90-6/93)

35. Lurie, Keith G. — Cardiovascular
Nicotine & the heart: potential link to sudden death
$225,000 (7/90-6/93)

36. Mcphee, Stephen — Intervention
Vietnamese smoking cessation intervention:a controlled trial
$707,559 (7/90-6/93)

37. Mitteness, Linda — Pub Health
Management of smoking by the elderly in long term care
$498,334 (7/90-6/93)

38. Moscicki, Anna-Barbara — Epidemiology
Effect of tobacco on cervical neoplasia in young women
$959,796 (7/90-6/93)

39. Otero-Sabogal, Regina — Intervention
Smoking prev. for hispanic pregnant&non-pregnant adolescents
$217,470 (7/90-6/93)

40. Palefsky, Joel — Epidemiology
Role of smoking in progression of anal neoplasia
$638,812 (7/90-6/93)

41. Parmley, William — Cardiovascular
Effects of passive smoking on experimental atherosclerosis
$340,594 (7/90-6/93)

42. Perez-Stable, Eliseo — Pub Health
Comparison of nicotine metabolism in four ethnic groups
$449,327 (7/90-6/93)

43. Piedimonte, Giovanni — Gen Biomed
Influence of cigarette smoke on neurogenic inflammation
$70,000 (7/90-6/92)

44. Pytela, Robert — Cancer
Integrin distribution and function in lung carcinoma cells
$358,128 (7/90-6/93)

45. Rempel, David M. — Epidemiology
The relationship of tobacco exposure to semen biomarkers
$186,739 (7/90-6/92)

Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

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Grant Awards by Institution

46. Rice, Dorothy P. — Pub Health
Cost of smoking in California
$110,697 (7/90-6/91)

47. Sagar, Stephen — Gen Biomed
Nicotine and early response gene expression in brain
$99,550 (7/90-6/91)

48. Scheinman, Melvin — Epidemiology
Cigarette smoking and sudden cardiac death
$783,631 (7/90-6/93)

49. Shipp, Miriam — Pub Health
Health services research
$65,120 (7/90-6/92)

50. Stewart, Anita — Pub Health
Health related quality of life outcomes of smokers who quit
$338,364 (7/91-6/94)

51. Strack, Alison — Gen Biomed
Nicotine, paraventricular nuclei and corticosteroids
$62,494 (7/91-6/93)

52. Walsh, Margaret — Intervention
A smokeless tobacc cessationintervention: college athletes
$648,997 (7/90-6/93)

53. Yen, Tien-Sze — Gen Biomed
Polycyclic aromatic hydrocarbons and hepatitis B virus
$75,000 (7/91-6/92)

AWARD # 1RT 560 AWARD PERIOD July 1, 1990 to June 30, 1993

PRINCIPAL INVESTIGATOR Nancy E. Adler

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Pregnant Smokers: Predictors of Cessation and Relapse

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this research is to examine the role of psychological and social factors in smoking cessation during pregnancy and postpartum. We have developed a theoretical model which includes four major predictors of quitting smoking during pregnancy and of remaining abstinent during the postpartum period: (1) Constructive thinking, the extent to which the woman deals effectively with stress, (2) Self-efficacy, the woman's belief in her own ability to quit smoking and maintain abstinence, (3) Attitude and perceived social expectations regarding smoking and quitting, and (4) Habit strength, reflecting the woman's psychological and biological dependence on tobacco. Secondary objectives in this research are to assess alcohol use in pregnant smokers and to examine the role of the woman's feelings about her pregnancy. Our overall goal is to use these data to design an intervention to prevent substance use and relapse during pregnancy and after.

We have implemented procedures to obtain basic demographic data and smoking status on all new obstetrics patients in 5 clinical study sites. From these, 266 women are being recruited if they: (1) are 16 years of age or older, (2) are in the first trimester of pregnancy and plan to carry to term, (3) have smoked at least daily for one week within a month of (2 weeks before to 2 weeks after) having a confirmed pregnancy test (4) have only known about the pregnancy for 2 weeks. The women are being interviewed during the first trimester of pregnancy, at 7 months gestation and again at 6 months postpartum to assess smoking status and psychosocial characteristics.

AWARD # 1RT 601 AWARD PERIOD July 1990 - June 1991

PRINCIPAL INVESTIGATOR Brian A. Gaese, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Oxygen Effects on Flow & Function in Ischemic Myocardium

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Heart attack (myocardial infarction) is caused by a relative insufficiency of blood supply to the heart (myocardial ischemia). Treatments which reopen blood vessels such as coronary bypass grafting and clot dissolution may salvage jeopardized myocardial tissue and decrease the morbidity and mortality of myocardial infarction. However, such treatments take time to work, and adjunctive measures to extend the viability and integrity of jeopardized heart tissue are necessary. One such adjunctive measure is the administration of supplemental oxygen. The objective of this project is to determine the magnitude, mechanisms and duration of the beneficial effects of supplemental oxygen in acute myocardial ischemia. The experiments in this project utilize an open chest swine model of myocardial ischemia in which a coronary artery is isolated and cannulated, and arterial oxygen tension is altered only in the coronary artery perfusing an ischemic myocardial zone. In this model, the effects of arterial oxygen on contractile function, regional metabolism and the distribution of myocardial blood flow are measured.

In the first series of experiments in the current project, the left anterior descending artery was cannulated and flow to this artery was finely controlled via a roller pump. At high and low coronary oxygen tension, we have measured regional myocardial function, blood flow and metabolism. High oxygen tension (hyperoxia) increased the contractile function of ischemic myocardium substantially. This increase in contractile function was mostly attributable to an increase in endocardial blood flow, which was caused by an oxygen-induced blood flow redistribution. Coronary hyperoxia also decreased the production of lactate, a marker of ischemic metabolism. These data demonstrate for the first time that increasing arterial PO_2 during acute myocardial ischemia improves both function and flow distribution in the ischemic myocardium and decreases the metabolism of glucose as substrate.

In another series of experiments, we are examining the effects of high arterial oxygen tension on the autoregulation of coronary blood flow. Autoregulation is the physiological process which keeps coronary blood flow relatively constant over a wide range of coronary blood pressures. In these experiments, we have found that high arterial oxygen tension decreases blood flow to normal myocardium across a wide range of coronary pressures. This decrease in blood flow occurs without any apparent detrimental effects on contractile function, which suggests the hypothesis that oxygen use is more efficient during hyperoxia. This hypothesis and alternative hypotheses to explain this interesting finding will be tested in future experiments.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtw0000

AWARD # KT 47 AWARD PERIOD 1990-91

PRINCIPAL INVESTIGATOR Mary Croughan-Minihane

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Smoking Intervention for Women Seen in Primary Care Practice

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Physicians must help women patients stop smoking, maintain their weight following smoking cessation and put the risks associated with gaining small amounts of weight in perspective. In order to assist physicians in their efforts and to encourage smoking cessation among women, it is necessary to determine both physician and patient perceptions of barriers to smoking cessation and weight maintenance as well as effective methods for overcoming these barriers. To accomplish this, we plan to interview physicians and their female patients between 20 - 60 years of age. Although we originally proposed to interview physicians during year 1 of the study and to interview patients during year 2, it was determined that physicians and their patients needed to be interviewed simultaneously, thus preventing physician participation in the study from influencing patient responses. We have recruited 45 practice-based primary care physicians in northern California to participate in this study, all of whom have agreed to provide access to patient files. Additional phone calls and mailings are currently being done to increase the number of participating physicians to a minimum of 50. Both physician and patient data collection instruments are being reviewed by experts in the field and will be pre-tested on non-participating physicians as well as women who are current and former smokers. Physician and patient interviews are expected to begin in September, 1991 and to be completed by June, 1992. Information from the physician and patient interviews will be published and then used to develop a program which is effective in both smoking cessation and weight maintenance among women patients of primary care physicians. By achieving success in smoking cessation and weight maintenance for women, ultimate achievements will be seen in reduction of risk for coronary heart disease and cancer.

AWARD # KT 71 AWARD PERIOD July 1, 1990- June 30, 1993

PRINCIPAL INVESTIGATOR David J. Erle, MD

INSTITUTION University of California, San Francisco

TITLE OF PROJECT EFFECTS OF CIGARETTE SMOKING ON LEUKOCYTE ADHESION MOLECULES.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Emphysema is among the most common diseases caused by cigarette smoking. It is widely believed that emphysema is caused by the release of destructive enzymes from inflammatory cells (leukocytes) within the lung. It is well established that cigarette smoking causes a dramatic increase in the number of leukocytes in the lung. This project is designed to help determine how smoking leads to lung inflammation.

Leukocytes enter the lung from the bloodstream. The first step in the process involves the adherence of the leukocyte to the blood vessel wall (endothelium). A number of proteins on the surface of leukocytes are now known to be play a role in adherence to endothelium. These proteins are called leukocyte adhesion molecules. This project will examine whether cigarette smoking causes a change in leukocyte adhesion molecule function.

During the first year of the project, we have implemented powerful techniques for the study of adhesion molecules in our laboratory. These techniques allow us to measure the numbers of adhesion molecules expressed on leukocytes and to determine the function of these molecules. We have also identified a novel leukocyte adhesion molecule, designated as integrin $\alpha 4\beta 7$, which appears to have a role in inflammation.

Over the next year, we plan to obtain blood leukocytes from non-smoking and smoking volunteers and to study them with the techniques now in place in our laboratory. We hope to detect smoking-induced differences in leukocyte adhesion molecule function which may play a role in the development of emphysema.

AWARD # DA05552 AWARD PERIOD 07/01/90-06/30/93 Ass'd....

PRINCIPAL INVESTIGATOR Barbara A. Dodson, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Effects of Sedatives on Neuronal Nicotinic Binding

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Our overall objective is examine possible biochemical mechanisms underlying nicotine addiction. Brain nicotinic acetylcholine receptors (nAChR) are implicated in both the behavioral effects and addictive properties of nicotine. Therefore, our focus is two-fold: (1) to examine the effects of mood-altering drugs on nicotine binding to neuronal nAChR; and (2) to explore the underlying molecular biology of these receptors with respect to their role within the central nervous system (CNS).

We are examining drug-neuronal nAChR interactions using a rat brain synaptosomal binding assay. (Synaptosome are crude vesicular membranes prepared from cerebral cortex homogenates containing neuronal synapsic elements). We found that chlorpro-mazine and thioraxine (major tranquilizers), diazepam and flunitrazepam (anxiolytics), secobarbital and pentobarbital (hypnotic sedatives), amitriptyline and imipramine (anti-depressants) and pentazocine (opioids) all decrease specific L-^{3}H-nicotine binding to neuronal nAChR. Although varying in efficacies, [100μM] of each compound decreased binding from control value by at least 50%. By contrasted, [100 μM] of the anticon-vulsants diphenylhydantion and carbamazepine produced <20% reduction in specific L-^{3}H-nicotine binding. These results suggest direct sedative-nicotinic receptor interaction(s) within the CNS. We are now performing a more detailed examination of these drug-neuronal nAChR interactions to determine whether they represent specific (i.e., competitive or allosteric) or non-specific (i.e., hydrophobic) mechanisms of action

Neuronal nAChR represent a family of different nicotinic receptor subtypes. There-fore, we are developing systems for examining specific subtype pharmacology. Specif-ically, we are preparing the appropriate cDNA plasmids for cloning the subunit combin-ations $\alpha 3\beta 2$, $\alpha 3\beta 2$, $\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 3\beta 4$, and $\alpha 4\beta 4$. We have also begun to transfect *cos* cells (a mammalian cell line capable of transient receptor expression) with these plasmids. Preliminary experiments using this cloning system have resulted in the successful expression of the $\alpha 3\beta 4$ neuronal nAChR subtype in the cos cells.

Insight into how drug-nicotine interactions can change postsynaptic excitatory responses would aid in the understanding the behavioral effects of nicotine. By determining structural specificities for these drug interactions, compounds could be developed to enhance or inhibit these properties and perhaps provide a pharmacological intervention for nicotine addiction.

AWARD # Grant # RT 485 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Virginia L. Ernster, Ph.D. (Co-PI: Deborah Grady, M.D.)

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Cigarette Smoking and Facial Wrinkling

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Preliminary studies have reported that cigarette smoking is associated with prominent facial skin wrinkling. If confirmed, such findings could potentially have great impact in motivating young people not to smoke. If former smokers are shown to have less wrinkling than current smokers, older smokers might be motivated to quit. We are examining the association of cigarette smoking and facial wrinkling among 300 never smokers, 300 current smokers and 500 former smokers. Cigarette smoking and potential confounding variables are being assessed by questionnaire. Facial wrinkling is being measured using three methods: 1) a wrinkle score determined from facial photographs; 2) a wrinkle score determined by visual assessment; 3) optical profilometry, a laser-based scanning procedure.

The study was funded by the University of California Tobacco-Related Disease Research Program in the fall of 1990. After funding began, three research assistants and a computer programmer were hired and underwent extensive training on the study protocol. The three research assistants were instructed in recruitment, administration of the questionnaires, visual assessment of wrinkles, standardized photography of the crow's feet, forehead and perioral areas of the face and preparation of silicone casts of the crow's foot area for optical profilometry. A complete methods manual was prepared and revised and all study methods were pilot tested in 10 persons.

Subject recruitment began with mailings and telephone contacts in January, 1991. About 80% of persons identified from among Kaiser Permanente Health Plan Members who had a multiphasic examination in 1991 were eligible for the study and about 60% of those eligible have enrolled. To date, data entry is complete for 355 study participants. As planned, our stratified recruitment methods have resulted in a reasonably balanced number of subjects by each age, sex and smoking cell. We will continue to enroll subjects until the planned sample size is obtained. We are presently in the process of data entry and editing and will begin preliminary analyses soon.

Evidence that cigarette smokers look older than nonsmokers or that former smokers look younger than continuing smokers could alter the psychosocial desirability of cigarette smoking and play an important role in prevention and cessation efforts.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # R7446 AWARD PERIOD 7/1/90-6/30/93

PRINCIPAL INVESTIGATOR Walter E. Finkbeiner, M.D., Ph.D

INSTITUTION University of California, San Francisco

TITLE OF PROJECT In Vitro Characterization of Human Airway Gland Cells

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this proposal is to develop human tracheobronchial gland cell cultures which maintain differentiation, that is, function the same way grown in the laboratory as in the body. Tracheobronchial glands are composed of serous and mucous cells. These cells produce most of the mucus that protects the lung. However, in many chronic obstructive lung diseases including tobacco-induced chronic bronchitis, secretion from gland cells increases abnormally, and lung mucus builds up. Treatment for these diseases is often only symptomatic. However, before pathologic changes in airway secretion can be treated rationally, mucus secretion in healthy human airways must be better understood. Insights into the basis of normal airway secretion, resistance of airways to infections, and pathogenesis of diseases such as chronic bronchitis can be expected as human tracheobronchial gland cell preparations become available. Thus, the knowledge gained from these studies may help in understanding lung diseases such as chronic bronchitis, potentially allowing improvements in medical therapy.

In year one of this grant, factors which support gland cell growth have been identified: transferrin, triiodothyronin, hydrocortisone, insulin, endothelial cell growth supplement, epidermal growth factor and retinoic acid. The cells express serous and mucous cell-specific antigens. Production of mRNA for both lactoferrin, a serous cell-specific marker and mucin, a mucous cell-specific marker is detectable using the polymerase chain reaction. Cell secretions have been separated into glycoprotein and proteoglycan species using gel filtration chromatography. O-linked glycoproteins are being analyzed using high pH anion-exchange chromatography, and oligosaccharide maps are being prepared. As in the body, the cultured gland cells release secretions in response to adrenergic and cholinergic stimulation. Using a cell culture insert system and modified Ussing chambers, the electrical properties of tracheobronchial gland cell monolayers have been measured. It has been shown that cultured gland cells produce epithelial sheets of high electrical resistance, and that these cells can be induced to secrete Cl by a variety of agents. It is anticipated that cultures of passaged tracheobronchial gland cells grown on permeable supports will prove highly useful for studying mucus secretion.

AWARD # FT 85 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR David Hardman, Ph.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Smoking and Lipoprotein-Based Mechanisms of Atherogenesis

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Background: Atherosclerosis is a leading cause of mortality and morbidity in the U.S. at the present time. Current hypothesis holds that a key process in the development of atherosclerosis involves oxidative modification of lipoproteins within the artery wall. The modified lipoproteins are then recognized by scavenger receptors on macrophages and smooth muscle cells leading to rapid endocytosis and uncontrolled accumulation of cholesterol by these cells. Recent evidence suggests that components in tobacco smoke may induce or accelerate oxidative modification of lipoproteins, thus providing a plausible explanation for the increased risk observed in smokers for the development of atherosclerosis.
Objective: Oxidative modification of low density lipoprotein (LDL) chemically alters both the lipid and protein components of the particles. However, the recognition of modified LDL by scavenger receptors appears to be mediated by the protein component, apolipoprotein B (apoB). The long range objective for this project is the identification and characterization of structural elements on apolipoprotein B of modified LDL that are recognized by scavenger receptors.
Findings: In this investigation, it has been shown that oxidized LDL containing only the amino terminal half of apoB can compete for scavenger receptor binding as effectively as lipoproteins containing full length apoB. Thus, it appears that the site recognized by scavenger receptor is located, at least in part, in the amino terminal half of apoB and that the amino terminal half of apoB is sufficient to account for the receptor binding activity of oxidized LDL. The role of the carboxyl half of apoB is uncertain at this time. In addition, it has been found that fragmentation of apoB that is observed during oxidation does not generate detectable amino termini, suggesting that peptide bond cleavage is not involved. Thus, it appears that the fragmentation may involve cleavage through individual amino acids rather than between them.

AWARD # 1 RT 520 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Stanton A. Glantz, Ph.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Tobacco Industry Response to Passive Smoking

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This project seeks to study direct political activities by the tobacco industry to maintain the social acceptability of smoking in the face of growing scientific evidence that passive smoking is dangerous to nonsmokers, efforts to organize smokers as a cohesive force, efforts to reinforce smoking as socially acceptable among smokers, and the presentation of smoking as socially acceptable behavior in cigarette advertising and subliminal advertising such as through the encouragement of smoking in television and motion pictures. These general goals are being met through 5 interrelated projects. (1) Monitor and analyze tobacco industry publications for indicators of changing strategies for dealing with environmental tobacco smoke (ETS) and develop public health counter strategies. To meet this goal we are analyzing scientific meetings sponsored by the tobacco industry to counter agencies such as the US Environmental Protection Agency. (2) Preparation of in-depth case studies of tobacco industry activities relating to nonsmokers' rights and the response of the health community. This year we analyzed campaigns in Los Angeles, Sacramento and Lodi. This experience suggests that the determining factor in a campaign for tobacco control is the level of effort made by the pro-health forces rather than the magnitude of the tobacco industry's opposition. (3) Monitor and analyze presentation of smoking and nonsmoking in television and motion pictures, including brand identification. We area analyzing a random sample of films for the last 31 years for the presence and context of tobacco use. (4) Monitor and analyze presentation of environmental tobacco smoke in cigarette advertising. (5) Monitor and analyze tobacco industry political activity at the state-wide level. We have collected and published a detailed analysis of campaign contributions to the state legislature, state constitutional officers, state propositions, and lobbying since 1986. These data show that tobacco industry activities in California state politics have increased by a factor of 8 since 1986. The report, Political Expenditures by the Tobacco Industry in California State Politics, has attracted broad attention throughout the public and private sector and the media in California and elsewhere. It also provides background for our continuing analysis of the fate of specific legislation relating to tobacco control before the state legislature.

AWARD # IRT 475 AWARD PERIOD 1990-91

PRINCIPAL INVESTIGATOR Marc Hellerstein, M.D., Ph.D.

INSTITUTION University of California, San Francisco and Berkeley

TITLE OF PROJECT Substrate cycles, caloriogenesis and smoking cessation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to understand why some people gain weight after cessation of cigarette smoking and whether this process can be prevented by targeted metabolic interventions. The central questions are whether weight gain is due to increased calorie intake or decreased energy expenditure. Many people believe the former explanation but most research studies support the latter. We are studying normal smokers in a metabolic ward setting during a smoking period, after cessation of smoking for a week and on return after cessation of smoking for a longer period (5 weeks). Each subject is being intensively studied using state-of-the-art stable isotopic methods and nutritional evaluations. The specific metabolic questions being asked are, first, does smoking primarily increase energy expenditure or decrease caloric intake? Second, are changes in expenditure due to energy-wasteful breakdown and resynthesis of fats or glucose which in turn are caused by the adrenalin-releasing effects of nicotine? Third, do changes in expenditure persist over 5 weeks of non-smoking? Fourth, does smoking adversely affect cholesterol and triglyceride metabolism in an atherogenic manner? And finally, can these undesirable effects be blocked using metabolic inhibitors? We spent the first few months perfecting several of the novel metabolic techniques in pilot studies and have since enrolled 6 subjects for the 7-week study. Data is being generated successfully on each of the questions noted. Thus, for the first time, cholesterol synthesis, the fate of fatty acids, gluconeogenesis and other cellular processes have been measured in humans, and the effect of smoking on these pathways is being established. We expect to be well advanced towards resolving the first four specific hypotheses listed above over the next 6-12 months. We then hope to test metabolic interventions.

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AWARD # 1RT 169 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Peyton Jacob, III, Ph.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT CLINICAL PHARMACOLOGY OF TOBACCO ALKALOIDS

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to develop methods for determining exposure of smokers and smokeless tobacco users to certain nicotine-related substances known as tobacco alkaloids. The emphasis is on those alkaloids that may contribute to the biological effects of tobacco, that may be converted to cancer causing substances in the body, or may be useful as markers of tobacco use. Since these substances are specific to tobacco, determining their concentrations in biologic fluids (blood, urine, saliva) should be useful in assessing tobacco consumption. Currently, nicotine and its metabolite cotinine are the best markers for tobacco exposure, but they are not valid markers in persons using nicotine-containing medications such as nicotine gum or transdermal patches. Concentrations of tobacco alkaloids other than nicotine should be valuable for estimating tobacco exposure and assessing the efficacy of smoking and smokeless tobacco cessation programs.

During the past year we developed methodology for measuring concentrations of the alkaloids anabasine and anatabine in urine of smokers and smokeless tobacco users. Using this methodology, we determined urinary excretion of anabasine and anatabine in six smokers, six smokeless tobacco users, and in three smokers who used nicotine gum while abstaining from tobacco. Readily measurable concentrations of both alkaloids were found in urine of all tobacco users, with concentrations being significantly higher in urine of smokeless tobacco users. None of the three persons using nicotine gum excreted measurable amounts of anatabine; one of the three excreted a small amount of anabasine, presumably due to previous smoking. Our studies indicate that concentrations of anabasine and anatabine will be an objective measure for determining the success of smoking and smokeless tobacco cessation programs, including those in which nicotine gum or transdermal patches are employed.

AWARD # KT 40 AWARD PERIOD 1990-1991/YEAR 1

PRINCIPAL INVESTIGATOR SURINDER KAUR

INSTITUTION UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

TITLE OF PROJECT MASS SPECTROMETRIC STUDIES OF TOBACCO SPECIFIC ADDUCTS WITH HEMOGLOBIN

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Tobacco smoke contains a number of compounds that are known to cause cancer in animal models. Of these cancer-causing compounds, nitrosamines derived from the nicotine in tobacco are potent carcinogens and have been detected in tobacco smoke and saliva from smokers. Unlike many other carcinogens in tobacco which are also common ionic chemicals in the environmental, the nitrosamines NNK [4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone] and NNN [N'-nitrosonornicotine] are derived only from nicotine. Therefore these nitrosamines and their effects in smokers can potentially be linked specifically to tobacco smoking. In order to explore methods for identifying humans at increased risks of developing cancer from exposure to such potential cancer-causing compounds in tobacco, it is essential to study the effects of specific chemicals at the molecular level.

Cancer-causing chemicals are widely believed to bind irreversibly to molecules *in vivo*, such as DNA and blood proteins and this is the first step in a process which may eventually lead to cancer. Therefore, the structures of DNA or proteins that have been altered in this way can give information about specific chemicals that may be important in causing cancer. The major goal of this project is to identify modification of the structure of human hemoglobin which has been reacted with the nicotine-derived compounds NNK and NNN using state-of-the-art mass spectrometry. The recently developed electrospray mass spectrometry method will be used to establish binding using the intact protein level by mass shifts in the molecular weight of hemoglobin. High resolution liquid secondary ion mass spectrometry and four sector tandem mass spectrometry will be used to determine the structures. Studies *in vitro* will aim to develop protocols for the quantitation of hemoglobin adducts at physiologically relevant levels to aid in studies of alkylated hemoglobin from heavy tobacco smokers.

The first year of funding has involved obtaining mass spectrometric data for native human hemoglobin to be used as standard references for the data which will be obtained for modified hemoglobin later. A variety of protocols have been used (HPLC purification, enzymatic digestion, HPLC isolation and mass spectrometry). Preliminary experiments have been undertaken to optimize conditions for the formation of hemoglobin modified *in vitro* with metabolites of NNN using P-450$_{IIB1}$ for metabolic activation.

AWARD # KT 177 AWARD PERIOD FY 1990-1993

PRINCIPAL INVESTIGATOR John P. Kane, M.D., Ph.D.

INSTITUTION UCSF

TITLE OF PROJECT Effects of Smoking on High Density Lipoprotein Species

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cholesterol, and other fatty molecules are carried in human blood in complexes with proteins (lipoproteins). Whereas some lipoproteins appear to carry cholesterol into artery walls, causing atherosclerosis (hardening of the arteries), high density lipoproteins (HDL) appear to have some protective effect against this process. Using a new technique developed in our laboratory, we have found the HDL are a population of eight to ten distinct species. Our research is directed at characterizing these species and determining their functions in the body, especially with respect to their protective effects. It is known that smoking decreases the total level of HDL in blood. We are determining which HDL species are affected and measuring the functional consequences of the reduced levels of HDL. To date, we have isolated five species, and have shown that one of them is able to remove surplus cholesterol from cells.

AWARD #: RT 589 AWARD PERIOD: July 1, 1990–June 30, 1991

PRINCIPAL INVESTIGATOR: Philip R. Lee, M.D.

INSTITUTION: Institute for Health Policy Studies, UCSF

TITLE OF PROJECT: Prop 99 & Indigent Care: Lessons for Future Health Care Reform

This project is a process evaluation of the implementation of the indigent care provisions of Prop 99/AB75. The purpose of the project is to assist the California State Legislature, the Health and Welfare Agency, the Department of Health Services, California's counties, the voters of California, and others concerned about health care for the indigent in understanding the implications of Prop 99/AB 75 for future health care reform. The objectives of the project are: (1) to investigate state and county implementation of indigent care provisions of Prop 99/AB75 and subsequent clean-up legislation; (2) to describe the effect of implementation of Prop 99/AB 75 provisions on the organization, delivery, and financing of indigent care services in counties; and (3) to analyze the implications for future health care reform. Findings from the first year of this study show that: (1) Prop 99 and AB 75 are complex measures, with multiple goals for indigent care designed to serve the interests of multiple stakeholders, including state administrative agencies, counties, public hospitals, private hospitals, private physicians, advocacy groups, and persons without access to health care; (2) the implementation of indigent care provisions of Prop 99/AB 75 has been a slow process for both the state and counties; and (3) primary program and fiscal data are still unavailable at the state and county levels related to many aspects of implementation, including information from Fiscal Year 1989-1990, the first year of implementation of indigent care provisions. Preliminary findings from pilot case studies of implementation conducted in five California counties (Sacramento, Napa, Alameda, San Francisco, and Santa Cruz) provide a more detailed picture of progress and problems in implementation in relation to the goals of Prop 99/AB 75 for indigent care.

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AWARD # 279 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Hakon Leffler

INSTITUTION University of California, San Francisco

TITLE OF PROJECT An endogenous Lectin in Airway Epithelium and Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The mucosal cells lining the human airways are the main target of damage caused by tobacco smoke. The most serious result of that damage is lung cancer. The goal of this project is to understand one aspect of the function of the airway mucosa at the molecular level and how it is disrupted in disease caused by tobacco.

We have identified a protein, L-29, which is abundant in the airway mucosa. The protein is interesting because it is a carbohydrate binding protein, lectin. As such it may interact with components of mucous that increase drastically in quantity in some conditions such as chronic bronchitis. Other complex carbohydrates express specific structures in lung cancer. L-29 is also expressed in lung cancer and has recently been shown (by others) to increase malignancy in experimental tumors.

This first year of the project we have characterized the structure of L-29. This has been done both for the amino acid sequence and for the DNA that encodes the protein. This has helped us understand how some of the multiple molecular forms of L-29 are generated. In particular it appears to interact with the enzyme, 92 kDa collagenase, that increases in invasive cancers. Next, we have generated tools for further study of L-29. One tool is antibodies directed against the protein to be used for detection in tissue sections and cultured cells. Another tool is the protein itself produced in bacteria by genetic engineering techniques. This will greatly facilitate the study of its properties and the carbohydrates it bind to since it is very difficult to isolate useful amounts from tissue. Finally we have established the feasibility to study L-29 in a common model system for polarized epithelia. In this we have demonstrated apical secretion. This suggests that in the lung part of the lectin may be secreted into the lumen of the airways.

AWARD # 1RT 355 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Jon D. Levine, M.D., Ph.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Nicotine Enhanced Adrenal Medullary-Dependent Inflammation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of the project is to investigate mechanisms by which nicotine consumed in tobacco smoke could lead to an aggravation of diseases in which inflammation plays a part, such as bronchitis, asthma, arthritis, colitis and others. Nicotine is known to increase levels of adrenaline, and adrenaline is known to increase tissue injury during inflammation, by action on the sympathetic nervous system. The study described below investigated the effect of administered nicotine on a model of inflammation in the knee joint produced by the sympathetic nervous system by a substance found naturally at sites of inflammation. Bradykinin causes fluid to leak from blood vessels, which leads to swelling. We have found that this swelling, although present when there is inflammation, seems to decrease the amount of actual injury to cells that occurs, probably by diluting the factors that hurt the cells the most. We found that extremely small amounts of nicotine (given by a subcutaneous injection) very significantly lowered this protective mechanism. We also found that when the adrenal medulla, which makes epinephrine, was removed nicotine had much less effect, indicating that it is indeed through the effect of nicotine to increase epinephrine that the effect on swelling occurs. We also showed that the nicotine effect is a specific physiological effect mediated by a receptor by using a drug that acts very specifically to antagonize the action of nicotine at its known receptor. Finally, we performed an experiment in which we administered this antagonistic drug to one knee and compared the experimental data to the other knee and showed that nicotine did not seem to have an action at the knee itself.

These findings provide a firm basis by which nicotine could increase inflammatory injury, a mechanism that can explain the known effects of smoking to aggravate arthritis and bronchitis. Also, by studying the dose needed and knowing the levels that occur in smokers and passive smokers, we found that the nicotine effect on inflammation would be expected to be exerted in passive as well as active smokers. Study is planned to further characterize this mechanism and it is hoped to provide new therapeutic modalities for diseases aggravated by smoking.

AWARD # KT 75 AWARD PERIOD July 1, 1990- June, 30, 1991

PRINCIPAL INVESTIGATOR Keith G. Lurie, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Nicotine and the Heart: Potential Link to Sudden Death

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Over 400,000 Americans die yearly from sudden cardiac death. Although cigarette smoking is an independent risk factor for sudden death, a definitive biochemical link between smoking and sudden death has remained elusive. Nicotine stands at center stage as a potential cause of malignant and often fatal cardiac arrhythmias. This toxic chemical causes a number of complex, yet profound, cardiac effects. Many, if not all, of these effects are thought to be secondary to nicotine receptor-mediated release of the neurotransmitters. Most of the studies to date on the mechanism of nicotine-induced cardiac toxicity have focused on acute release experiments. Much less is known about the cardiac effects of more chronic nicotine exposure, particularly as a cause of sudden cardiac death. The objective of this project is to study the effects of chronic nicotine infusion on cardiac electrophysiology and biochemistry. In the first year we have focussed on developing a rabbit model to study the effects of long-term exposure of nicotine on cardiac biochemistry. Minipumps containing high concentrations of nicotine were implanted subcutaneously into rabbits. Nicotine was released slowly over several weeks. We found this method to be a reasonably reliable way to achieve nicotine levels similar to those measured in heavy smokers. We used this model to study the effects of nicotine on receptors in the heart for adrenalin (B-adrenoceptor) and other processes (adenylate cyclase activity) associated with this receptor. In addition, we developed a new method to measure cAMP, a secondary messenger which is released when adrenalin receptors are stimulated. This new microanalytic technique will enable us to study the effects of nicotine on the conduction system within the heart. Finally, we studied the effects of nicotine on the way the heart burns fuel. We found that although there was no change in the B-adrenoreceptor number, there was a surprising increase in adenylate cyclase sensitivity to adrenalin in hearts exposed to chronic nicotine. Furthermore, there appears to be a decrease in glycogen, one of the intrinsic fuels for the heart, after long-term exposure to nicotine. Thus, hearts exposed to chronic nicotine appear to have a surprising increased sensitivity to adrenalin after nicotine exposure as well as a decrease in fuel supply. These changes may make hearts from smokers more susceptible to arrhythmias and sudden cardiac death.

AWARD # RT 48 AWARD PERIOD July 1, 1990-June 30, 1993

PRINCIPAL INVESTIGATOR Stephen J. McPhee, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT "Smoking Cessation in Vietnamese: A Controlled Trial"

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

In previous studies, we have found that 39-56% of Vietnamese men currently smoke cigarettes (compared to 26% of men in the general California population). Vietnamese men, therefore, have a higher risk of developing tobacco-related diseases such as cancer, heart disease and chronic lung disease. We are conducting a three-year trial of a multicomponent community-based smoking cessation intervention among Vietnamese men living in Santa Clara County, California. To date, we have developed and applied several different culturally-sensitive intervention methods and materials to the intervention community, including: community awareness activities (Vietnamese-language health education materials (brochures, self-help quit kit, posters, bumper stickers, buttons), public speeches, videotape broadcast, and print media and television counteradvertising), and support and training activities (professional education in smoking-cessation counseling for Vietnamese physicians). The effectiveness of the intervention will be evaluated by two community surveys of randomly selected Vietnamese men conducted both before and after the 18-month intervention period. These telephone surveys are being conducted in both Santa Clara County, California (the community receiving the intervention) and Houston, Texas (a community not receiving the intervention). We have completed pre-intervention surveys of 1,322 Vietnamese men in Santa Clara County and 1,581 Vietnamese men in Houston. Preliminary analysis of the data shows the following smoking prevalences: in Santa Clara County (intervention site), 36% of respondents are current smokers, 20% are former smokers, and 44% are never smokers, and in Houston (control site), 40% are current smokers, 14% are former smokers and 46% are never smokers. Planned future intervention activities include: a Vietnamese-language smoking cessation class, and environmental change activities including measures to promote smoke-free environments in Vietnamese businesses and worksites. Planned future evaluation activities include conduct of the post-intervention telephone surveys in the two communities to assess the impact of the intervention.

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AWARD # 1 RT 547 AWARD PERIOD Yr 01 July 1, 1990-June 30, 1991

PRINCIPAL INVESTIGATOR Linda S. Mitteness, PhD

INSTITUTION University of California San Francisco

TITLE OF PROJECT Management of Smoking by the Elderly in Long Term Care

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This three year semi-longitudinal study investigates the adjustment of elderly smokers and non-smokers to life in a long-term care institution with a moderately restrictive smoking policy. Currently, very little is known about smoking in skilled nursing facilities, even though smoking is very common there and created many dilemmas, the most salient of which concern (a) weighing the rights and needs of both smokers and non-smokers and general safety (especially in relation to fire) issues, and (b) balancing the institution's mandate to protect the health of its patients with the residents' freedom to smoke in their own home.

Using an anthropological approach, we are: (1) observing the smoking behavior of residents in both public and private space in a large long-term care facility in San Francisco, CA; (2) interviewing 88 nursing staff, 10 physicians, 10 pastoral counselors/social workers, and 10 housekeeping staff about caregiving and the management of smoking, especially in relation to demented residents; (3) observing, and interviewing 200 new, elderly (aged 65 or more) admissions, both smokers and non-smokers, three times over a six month period, about their adjustment to the facility's smoking environment; and, (4) evaluating, through non-invasive biological tests, change over six months in subjects' direct or indirect (environmental tobacco smoke) exposure to smoke.

Preliminary analyses of data from this study reveal that smoking is a major focus of social interaction between residents; that administrators and physicians are very aware of the tension between collective safety and health and individual autonomy; that caregiving staff regard assisting residents to smoke as a legitimate part of their care plan.

The study is on-going. Data are still being gathered and will be analyzed in detail later.

AWARD # RT 487 AWARD PERIOD 7/90 - 6/93

PRINCIPAL INVESTIGATOR Anna-Barbara Moscicki, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT The effect of tobacco on cervical neoplasia in young women.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The role of cigarette use in the development of cervical precancers and cancers remains highly controversial. Though researchers have linked human papillomavirus (HPV) infections with cervical cancers, evidence suggests that cigarette use or exposure is an important co-factor for the development of cervical intra-epithelial neoplasia (CIN) also known as dysplasia. This study proposes to 1) examine the role of cigarette use as a co-factor in the development of cervical intra-epithelial neoplasia (CIN) in a sexually active adolescent female population positive for HPV and 2) to examine the effect of cigarette smoking on the cervix immune system. Methods: 832 females ages 13-19 years and positive for HPV DNA will be asked to undergo a special examination using a colposcope. Those females with a positive test for HPV DNA test and no evidence of cervical neoplasia (N=480) will be asked to enroll in a longitudinal study. Patients will be examined at the initial visit and every 4 months or until CIN develops. Colposcopic examinations, cervical measurements for nicotine and cotinine (tobacco by-products), Pap smears, test for sexually transmitted diseases and cervical epithelial Langerhans cell studies (tests of the immune system), and face-to-face interviews for detailed information on cigarette use or exposure, sexual behaviors and contraceptive use will be performed at scheduled intervals. Four hundred HPV negative control subjects will be followed similarly for comparison. Results: To date, we have analyzed the first visit on 129 subjects. We have found that there is a trend association between smoking and abnormal Pap smears. Women who report ever smoking are more likely to have an abnormal Pap smear. Among those who have smoked, women who smoked greater than 5 years were more likely to have an abnormal smear compared to women who smoked less than 5 years. This study will describe the risk of developing CIN over the next 2-3 years associated with tobacco use or exposure. The results from this study will be related to the prevention and education of precancer lesions in young women as well as identifying a clinical model for the role of viral-nicotine interactions in abnormal cellular development.

AWARD # 1RT17 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Regina Otero-Sabogal, Ph. D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Smoking Prev. for Hispanic Pregnant and Non-Pregnant Adolescents

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The goal of this project is to develop a culturally-appropriate intervention to prevent initiation of cigarette smoking and to promote smoking cessation among pregnant and non-pregnant Hispanic adolescents by increasing awareness of smoking-related adverse health effects and the dangers of passive smoking to their children. The specific aims are: 1) To identify the cultural factors related to adolescents' perceptions of the risks of smoking and the effects of smoking on their offsprings and on their health by comparing the knowledge, attitudes, and smoking intentions of 200 Hispanic and 150 non-Hispanic White pregnant and non-pregnant adolescents between the ages of 13 and 18 years, who attend 12 Prenatal, Adolescent and Pediatric clinics and the Special Supplemental Food Program for Women, Infants, and Children (WIC) programs and community agencies in San Francisco. 2) Based on this research to develop a culturally-appropriate anti-smoking program that will promote prevention of smoking initiation for non-smokers, improve knowledge of the effects of passive smoking and encourage cessation and maintenance for current smokers among Spanish and English-speaking Hispanic pregnant and non-pregnant adolescents in San Francisco. 3) To evaluate the intervention by conducting pre and post measures of the changes in knowledge, attitudes and smoking habits of a sample of Hispanic adolescents attending the clinics participating in the program, compared to Hispanic adolescents attending clinics in which the intervention has not been implemented.

To identify smoking behaviors, key language expressions, attitudes and most appealing messages in the media, two focus groups were carried out with pregnant and non-pregnant Hispanic adolescents. Results suggest that adolescents are aware of the effects of cigarette smoking as well as the effects of passive smoking. The main influence leading to cigarette smoking was seeing a relative or a friend smoke. The adolescents were concerned about the effects of smoking on appearance, i.e., wrinkles, yellow hands and teeth, bad breath. Some of the reasons why adolescents smoke are because they are lonely and bored. Others do it because their peers smoke or because they want to impress others. Hispanic adolescents who are immigrants perceive their US born peers as very liberal, i.e., they do not respect their parents. The subjects also believed that there are differences in the way parents raise their children in the US in comparison with their countries of origin. These adolescents also perceived smoking as less dangerous than abusing drugs such as marijuana or cocaine. They also believed that young people go through a stage in life when they smoke but they will eventually outgrow this behavior. According to these groups, exposure to cigarettes is fairly easy. When asked about the characteristics of educational materials they would like, they gave information about what is most appealing to them.

A close-ended questionnaire in English and Spanish has been developed based on the content analysis of the focus groups and open-ended questions. Some measure smoking habits, knowledge, beliefs, attitudes, and social norms of cigarette smoking, other use of drugs, emotional well-being, access to educational materials, acculturation and demographics. Extensive pretesting of the questionnaire was carried out with English and Spanish respondents at site locations included in this study. Data collection has been initiated.

AWARD # 1RT 484 AWARD PERIOD 07/01/90-06/30/93

PRINCIPAL INVESTIGATOR Joel M. Palefsky, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Role of Smoking in Progression of Anal Neoplasia

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The incidence of anal cancer is increasing among homosexual males, and may be linked to the AIDS epidemic. Like cervical cancer, anal cancer has been linked to smoking. However, the role of smoking in the pathogenesis of these diseases is still poorly understood because of inadequate control for other potentially important cofactors in previous studies, such as infection with human papillomavirus (HPV) and immunosuppression. The specific aims of this study are: 1) to prospectively study the natural history of potentially precancerous epithelial abnormalities of the anus in a high risk population, and 2) to prospectively study the role of smoking and other cofactors in the incidence and progression of anal disease in this population.

To date, 135 homosexual men with Group IV HIV disease have been enrolled in the study. Results analyzed thus far indicate that 45% of the subjects had anal cytologic abnormalities. Thirty-five% of the subjects, 5% had condyloma, and 5% had AIN 1. Analysis of CD4 counts of these subjects indicates that the mean CD4 count of those with normal cytology was 306, compared to 198 for those with condyloma, 190 for those with atypia, and 88 for those with AIN. These results confirm that higher grade anal lesions are associated with more advanced immunosuppression as measured by CD4 counts. New subject enrollment is continuing, and we are now beginning to see subjects for their 6 month follow-up visit.

HPV data, as well as questionnaire data detailing smoking use and other potential cofactors has been collected by not yet analyzed; conclusions regarding the role of smoking and other cofactors will be made pending the analysis of these data. However, data analyzed thus far confirm the high prevalence of anal cytologic abnormalities and AIN among homosexual men with Group IV HIV disease. In addition, these data confirm the role of advanced immunosuppression in the pathogenesis of AIN as indicated by the association between AIN and a low absolute CD4 count.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

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Grant Awards by Institution

AWARD # 1RT-145 AWARD PERIOD November 1990 to July 1, 1991

PRINCIPAL INVESTIGATOR William W. Peralev, MD

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Effects of Passive Smoking on Experimental Atherosclerosis

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this study is to evaluate the effects of passive smoking on atherosclerosis in rabbits fed a high lipid diet. These past several months have been spent in developing the techniques for quantitating smoke exposure, purchasing the appropriate equipment, and identifying the space and special cages. Because UCSF is a smoke-free environment, this has complicated all of the above. In quantitating smoking exposure, we have evaluated carbon monoxide using two different analyzers and also have utilized a piezo balance to measure particulates in the air. This device has been used as the gold standard for measurements of particulate matter by the EPA. We have also obtained a passive monitor of vapor phase nicotine in the air which may also help to quantitate the smoking exposure. Passive smoke is produced by using a Borgwaldt smoking machine. We can analyze both side-stream smoking and mainstream smoke with this device. During the past few months we have overcome all of the major technical and environment difficulties which were required before starting this project and have obtained or borrowed the appropriate equipment to make the measurements. The actual experiments themselves have now begun and we will evaluate the effects of passive smoke on the development of atherosclerosis in the lipid-fed rabbit.

AWARD # FT 23 AWARD PERIOD 1990-1992

PRINCIPAL INVESTIGATOR Giovanni Piedimonte, M.D.

INSTITUTION University of California San Francisco

TITLE OF PROJECT Effect of cigarette smoke on neurogenic inflammation

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cigarette smoke stimulates sensory nerves in the airway mucosa causing local release of the inflammatory neuropeptides substance P and calcitonin gene-related peptide (CGRP). We examined whether these neuropeptides could influence blood flow in the airway microcirculation. In this study, we used the reference sample microsphere technique to measure changes in regional blood flow and cardiac output distribution produced in the rat by substance P, CGRP, and capsaicin, a drug that releases endogenous neuropeptides from sensory nerves. Three sets of microspheres labeled with different radionuclides were injected into the left ventricle of anesthetized F344 rats before, immediately after, and 5 min after left ventricular injections of either capsaicin (10^{-7} mol/kg), substance P (10^{-8} mol/kg), or CGRP (10^{-8} mol/kg). The reference blood sample was withdrawn from the abdominal aorta, and was simultaneously replaced with 0.9% NaCl at 37°C. Groups of rats were pretreated with atropine, guanethidine, and hexamethonium to inhibit autonomic reflexes. We found that stimulation of sensory nerves with capsaicin causes a large increase in microvascular blood flow in the extrapulmonary airways (498 ± 110% increase from baseline, mean ± standard error; $p < 0.01$), which does not occur in other organs. This effect of capsaicin was still present after the inhibition of autonomic reflexes and was mimicked by systemic injections of substance P (463 ± 160% increase; $p < 0.01$), whereas CGRP did not increase airway blood flow significantly (49 ± 29% increase; $p = 0.4$). Thus, inhalation of cigarette smoke is likely to induce large increases of airway blood flow by releasing substance P from sensory nerve terminals, and this may be a crucial component of cigarette smoke-induced inflammation of the respiratory mucosa.

AWARD # 1 RT 521 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR ELISEO PEREZ-STABLE

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Comparison of Nicotine Metabolism in Four Ethnic Groups

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

There is considerable evidence that nicotine is an important determinant of tobacco smoking behavior. Cigarette smokers appear to regulate their tobacco consumption to gain desired effects of nicotine which are related to the levels of nicotine in the body. The rate of metabolism of nicotine, and clearance of its principal metabolite cotinine, are important determinants of individual differences in self-reported consumption of nicotine from tobacco.

The objective of this project is to systematically evaluate the rate and pattern of nicotine metabolism and the relationship between metabolism and daily intake of nicotine in habitual smokers from four major racial/ethnic groups residing in California: U.S. born Non-Hispanic Whites or Caucasians, Blacks/African Americans, Latinos/Hispanics of Mexican or Central American background and Chinese Americans. This will determine the extent to which different metabolic rates exist in these ethnic groups and the possible relationship this may have to self-reported cigarette consumption. Although self-reported cigarette consumption is lower among Blacks, Latinos and Asians, other studies have raised issues of underreporting consumption and differences in metabolism of nicotine as possible explanations. This project will be definitive in answering these questions.

During the first year of this Project, 43 subjects have been studied: 22 Latinos, 13 African Americans and 8 Whites. No analyses of cotinine and nicotine have been conducted to date.

AWARD # 1 RT 338 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR Robert Pytela

INSTITUTION University of California, San Francisco

TITLE OF PROJECT INTEGRIN DISTRIBUTION AND FUNCTION IN LUNG CARCINOMA CELLS.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The long-term objective of this project is to characterize the role of a novel class of cell-surface receptors, termed integrins, in lung cancer metastasis. Integrins are found on the surface of all cells and are believed to play important roles in mediating and regulating a cell's interaction with its environment, which is composed of the surfaces of other cells as well as extracellular matrix proteins. It is likely that changes in the nature and the activity state of integrins on the surface of a tumor cell are closely associated with malignant transformation and metastatic progression. The current study is designed to characterize the kind of integrins that are present on different types of lung carcinoma, to analyze any changes that may be associated with tumor progression and metastasis, and to unravel the functional contributions of different integrins to the metastatic process. We have initiated this work by developing a novel technique that makes it possible to rapidly identify the integrin molecules present in a given lung carcinoma cell type. This is done by isolating the individual DNA molecules corresponding to the genetic information encoding these integrins. We have now established the application of this technique to both components, termed α and β subunits, that make up the functional integrin receptors. Using this technique, we have isolated pieces of DNA corresponding to 10 different α subunits and 7 different β subunits, several of which were previously unknown. These DNA molecules can be used to identify the presence of integrins in lung carcinoma cells cultured in the laboratory, as well as in sections of lung cancer tissue obtained from surgical specimens, using a technique called in situ hybridization. We have taken the first steps towards establishing this technique in our laboratory. To identify integrin proteins in cells and tissues, we have developed novel antibody reagents that bind to two previously unknown integrins, termed β6 and β7. We are also working on determining the complete coding DNA sequence of three novel α subunits, termed α7, α8 and αA. This will allow us to prepare antibodies to these molecules by immunizing rabbits with short synthetic pieces of the predicted protein sequence. We are beginning to apply these reagents to the analysis of a variety of lung carcinoma cell lines, as well as tissue samples from surgically removed lung carcinoma.

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Tobacco Industry Documents - https://www.industrydocuments.ucsf.edu/docs/mvvl0000

AWARD # RT 500 AWARD PERIOD 7/1/90 - 6/30/92

PRINCIPAL INVESTIGATOR David Rempel, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT The Relationship of Tobacco Exposure to Semen Biomarkers

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objectives of this study are to evaluate the relationship between smoke exposure and semen biomarkers and pregnancy outcome. Some studies have suggested that tobacco exposure is a toxin to sperm. However, these studies have been flawed in selection, bias and use of non-standardized tests for the measurement of sperm parameters. In this study approximately 220 "normal" couples who are at risk for pregnancy are being recruited from Kaiser, Santa Clara. The women partners are collecting daily urine samples to be analyzed for urine hCG and the male partners are providing two semen samples to be analyzed for sperm motion and sperm morphometry ("biomarkers"). This grant is funding the analysis of saliva and semen from the male partners to determine levels of cotinine and nicotine.

During the first year of the study, 185 men have been recruited as full participants to the study and 65 men have refused to participate. All of these men completed a long questionnaire and also provided two semen samples and one saliva sample. The semen and saliva samples have been frozen and are in storage at San Francisco General Hospital.

During the first two months of the next year we will complete recruitment of the male subjects (220). After all saliva and semen samples have been collected, they will be analyzed by GC-MS for cotinine and nicotine. The laboratory data and the data from the questionnaires will be entered into a computer data base and the relationship between the smoke exposure based on semen biomarkers and the questionnaires will be analyzed and compared to the semen biomarkers. By evaluating the relationship of semen biomarkers to objective measures of tobacco smoke and controlling for confounders, some insight will be gained into the effect of active and passive tobacco smoke exposure on the male reproductive function.

PRINCIPAL INVESTIGATOR Stephen M. Sagar, M.D.

CAMPUS/INSTITUTION U.C.S.F.

AWARD # 1RT-166 AWARD PERIOD 7/1/90 - 12/31/91

TITLE OF PROJECT Nicotine and Early Response Gene Expression in Brain

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 7".

This project is designed to identify brain nerve cells that undergo long-term changes in their cellular physiology in response to nicotine. In order to accomplish this, we administer nicotine to rats by intravenous injection and examine brain tissue for the presence of a specific protein called Fos. Under most conditions, very few nerve cells in the brain make this protein. However, when nerve cells are suddenly and powerfully stimulated, they make Fos, which can be detected with a specific antibody. By localizing nerve cells that make Fos after nicotine injection, we can identify at least a subset of strongly stimulated cells. Moreover, there is a great deal of evidence that the function of Fos is to regulate the type and amount of proteins made by a cell. Therefore, it is reasonable to assume that those nerve cells that make Fos after nicotine exposure are those cells that are induced to alter their pattern of protein synthesis, thereby adjusting their cellular physiology, in response to the drug.

Those few we have used large, single doses of nicotine. Nerve cells that are induced to make the Fos protein include many in the visual system of the brain. These areas are known to respond physiologically to nicotine. The time course, dose-response relationships and pharmacology of this response has been defined. It would be important to study lower doses of nicotine and repeated doses, to more closely simulate the effect of cigarette smoking. In addition, we are in the process of comparing nicotine with other addictive drugs, particularly stimulants such as amphetamine and cocaine in order to look for common features of the neuronal responses.

We believe we have identified one group of brain nerve cells that respond to nicotine by altering their cellular physiology. Because of the complex pharmacology of nicotine, further work will be necessary to determine if there are other groups of nerve cells that can respond under different circumstances. This approach has the potential to allow the detailed anatomic study of areas of brain that are involved in the response to, and perhaps addiction to, nicotine and other drugs of abuse.

AWARD # 1 RT 539 AWARD PERIOD 7/01/90 - 6/30/91 (request for no-cost extension to 12/31/91

PRINCIPAL INVESTIGATOR Dorothy P. Rice

INSTITUTION University of California at San Francisco

TITLE OF PROJECT Cost of Smoking in California

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

This research will estimate the current burden of smoking in California. Included are the direct and indirect costs of the health effects of smoking for California and for each of the 58 counties in California. The direct costs include amounts spent for hospital and nursing home care, physicians' and other professional services, drugs and medical supplies on behalf of people suffering from illnesses attributable to smoking. Indirect costs consist of morbidity and mortality costs. Morbidity costs are the value of lost productivity by persons unable to perform their usual activities due to smoking-related illnesses. Mortality costs are the value of lost productivity due to premature deaths resulting from smoking-related illnesses.

Considerable progress has been made toward the development of these cost estimates, but the research has not yet been completed. A variety of factors have caused the delay, including the late availability of the 1989 mortality data and the data on prevalence from the 1990 California Prevalence Survey conducted by John Pierce, UC San Diego. A six-month no cost extension has been requested to complete the research.

Major accomplishments to date include the estimation of 1988 mortality costs in California by county in collaboration with Dr. George Kaplan, California Department of Health Services, who is also conducting research under the Tobacco-Related Disease Research Program. A report on these mortality costs will be published by the California Department of Health Services. Following are some highlights from this forthcoming report:

- In 1988, a total of 42,177 deaths, or one out of five adult deaths and one out of 12 pediatric deaths in California were due to smoking;
- These deaths represent a total of 416,813 years of potential life lost or 9.9 years per smoking-attributable death;
- Productivity losses amount to $3.8 billion or $90,186 per smoking-attributable death;
- About three out of ten deaths (12,213) attributed to smoking in California occurred in Los Angeles with productivity losses estimated at $1.2 billion;
- Eight additional counties (Alameda, Orange, Riverside, Sacramento, San Bernadino, San Diego, San Francisco, and Santa Clara) had more than 1,000 deaths attributable to smoking.

AWARD # 1 RT 461 AWARD PERIOD July 1, 1990-June 30, 1991

PRINCIPAL INVESTIGATOR Melvin M. Scheinman, M.D.

INSTITUTION University of California, San Francisco

TITLE OF PROJECT Cigarette Smoking and Sudden Cardiac Death

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Each year sudden cardiac death from heart rhythm disturbances kill a population half the size of San Francisco, California. Smokers with known cardiac disease are known to be at an inordinate high risk from this phenomenon. We currently use non-traumatic means of identifying potential victims by recording electrocardiographic signals of the heart using skin applied surface electrodes. In order to detect smoking-induced heart rhythm disorders, we record a series of these non-traumatic electrocardiographic tests and apply them to smokers without heart disease, smokers with known heart disease, and smokers with known heart rhythm disorders. We have found that even smokers without heart disease developed changes in some of these tests. With smoking, abnormal subjects have more frequent test changes. Ultimately, we hope such non-traumatic tests will prove predictive of any future adverse heart disorder and thus allow early preventative intervention. To determine the mechanism of the smoking produced abnormal heart rhythm disorders, we have also performed invasive heart catheter tests in high risk smoking subjects to see if their heart rhythms become abnormal. Learning how and why, the heart can beat abnormally because of cigarette smoking allows for better treatment strategies. In the smoking patients when we found the heart beat became abnormal, the by-products of smoking were likely the responsible cause. If this result is further proved by more studies including long term patient follow-ups, we hope to identify those normal and abnormal patients at increased risk for sudden death and protect them from this disaster. We also suspect that even if smoking cessation is successful, there is a finite time after cigarette smoking is stopped when a high risk unstable heart beat state remains. Finding the best methods of patient protection during this vulnerable time is also a treatment goal.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # FT 8 AWARD PERIOD 7/90-6/91 Amt.....

PRINCIPAL INVESTIGATOR Miriam Shipp, MD, MPH

INSTITUTION Institute for Health Policy Studies, UCSF School of Medicine

TITLE OF PROJECT Fellowship in Health Services Research/Research: Break-even Point for Smoking Cessation Programs in Pregnancy

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 8.5".

Successful programs to help pregnant women quit smoking have been developed and evaluated, but formal smoking cessation programs are not a part of clinical care at most prenatal sites. The cost of such programs may be an issue. Considering the costs of adverse maternal and infant outcomes as a result of smoking, we theorized that there would be an amount of money a prenatal program could invest in smoking cessation for pregnant women and still "break even" economically. We used overall U.S. data on the prevalence of smoking, rates of smoking cessation, and incidences of poor pregnancy outcomes in a decision analysis to arrive at a "break even" cost of $32 per pregnant woman. When these data were varied to fit prevalence and incidence data from specific U.S. populations, the break-even costs varied from $10 to $237. Program planners and policy makers may use our analysis to guide economic decisions about smoking cessation programs for prenatal patients in their populations.

AWARD # RT574 AWARD PERIOD July 1, 1990-June 30, 1993

PRINCIPAL INVESTIGATOR Margaret M. Walsh

INSTITUTION University of California, School of Dentistry, San Francisco

TITLE OF PROJECT A Smokeless Tobacco Cessation Intervention: College Athletes

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 8.5".

The goal of our research is to increase smokeless tobacco (ST) cessation among college football and baseball athletes in California within a three-phased approach. In Phase I we have assessed the prevalence, patterns, correlates, and determinants of ST use, degree of addiction, and motivation to quit in this target population. In Phase II we are developing, based on questionnaire assessments, a ST cessation counseling message tailored to this group of athletes. The physician-initiated "Quit for Life" smoking cessation intervention model is being modified for delivery by dentists and dental hygienists as part of college athletic programs to help college football and baseball athletes quit using ST. In Phase III we will test the efficacy of the college-based ST cessation intervention that includes an oral examination, cessation advice from a dentist in conjunction with counseling by a dental hygienist on self-help quitting techniques. Fourteen colleges in California with baseball and football teams will be randomized to receive the cessation intervention or control condition.

One year after the completion of the intervention, efficacy will be determined by comparing biochemically confirmed quit rates as well as readiness to quit between intervention and control colleges. We anticipate that the intervention tested in this study will be effective in reducing the prevalence of use among college baseball and football players and be applicable to high school and junior high school baseball and football players.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

University of California, Santa Cruz

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:
1 $122,082

b) The subject of research grants by academic discipline:
Cancer = 1

c) The relationship between State and Federal funding for tobacco research:
0

d) The relationship between each project and the overall strategy of the research program :
see d) in Summary Data above

e) A summary of research findings:
see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:
0

g) The number and species of animals used in research:
N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":
N/A

Grant Recipient(s):

1. Konopelski, Joseph Cancer
Asymmetric synthesis of (-)-podophyllotoxin
$122,082 (7/91-6/93)

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

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Grant Awards by Institution

University of Southern California

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

24 $12,359,903

b) The subject of research grants by academic discipline:

Cancer	= 8
Cardiovascular Disease	= 3
Epidemiology	= 5
General Biomedical Sciences	= 2
Public Health, Public Policy, and Economics	= 1
Pulmonary Disease	= 1
Tobacco-Use Prevention, Intervention, and Cessation	= 4

c) The relationship between State and Federal funding for tobacco research:

Other State	= $172,247
Federal	= $6,277,069

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

7 $3,753,720

g) The number and species of animals used in research:

Guinea Pigs	= 150/year
Hamsters	= 90/year
Mice	= 532/year
Rabbits	= 3/year
Rats	= 900/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

8 $3,874,066

Grant Recipient(s):

1. Broek, Daniel Cancer
Structure-function studies of ras nucleotide-exchange-factor
$593,460 (7/91-6/94)

2. Cadenas, Enrique Cardiovascular
Phenols & PAH in tobacco-related cardiovascular disease
$422,606 (7/90-6/93)

3. Cote, Richard Cancer
Detection of lung cancer micrometastases
$120,346 (7/91-6/92)

4. Dent, Clyde Intervention
Tobacco cessation among pregnant low-income Latino women
$738,250 (7/90-6/93)

5. Dwyer, James H. Intervention
Physician incentives & smoking cessation effectiveness
$745,317 (7/90-6/93)

6. Fournier, Mario Pulmonary
Diaphragm cellular & functional adaptations to emphysema
$283,027 (7/90-6/93)

7. Gopalakrishna, Rayudu Cancer
Tobacco carcinogens/c-kinase oxidative activation/metastasis
$363,557 (7/90-6/93)

8. Hennigan, Karen M. Pub Health
Differentiating preadolescent/adolescent paths to smoking
$462,095 (7/90-6/93)

9. Hinton, David Gen Biomed
Effects of prenatal nicotine exposure on brain development
$750,522 (7/90-6/93)

10. Hiti, Alan L. Cancer
Tumor suppressor gene mutations in lung cancer
$333,053 (7/90-6/93)

11. Hofman, Florence Cardiovascular
Role of nicotine in endothelial cell function
$274,274 (7/90-6/92)

12. Kedes, Laurence Cardiovascular
Tobacco induced hypoxia: molecular genetic responses
$685,782 (7/91-6/94)

13. Landolph, Joseph Cancer
Tobacco carcinogen transformation of human bronchial cells
$621,667 (7/90-6/93)

14. Langholz, Bryan Epidemiology
Modifiers of susceptibility to smoking for lung cancer
$202,163 (7/91-6/93)

15. London, Stephanie J. Epidemiology
A genetic marker of lung cancer risk among blacks and whites
$1,037,143 (7/90-6/93)

16. Mack, Thomas Epidemiology
Tobacco-related disease in native California twins
$635,523 (7/90-6/93)

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Source: https://www.industrydocuments.ucsf.edu/docs/mtv00960

17. Martin, John — Cancer
Detection of lung tumor derived DNA in sputum using PCR
$115,098 (7/91-6/92)

18. Mazumder, Amitabha — Cancer
Novel approach to head and neck cancer therapy
$540,373 (7/90-6/93)

19. Pentz, Mary Ann — Intervention
Effects of social & personal coping programs for smoking prevention
$676,722 (7/90-6/93)

20. Ross, Ronald K. — Epidemiology
Environmental & genetic risk factors for bladder cancer
$1,149,699 (7/90-6/93)

21. Roy-Burman, Pradip — Cancer
Genetic aberrations in tobacco-related lung carcinogenesis
$214,339 (7/90-12/91)

22. Scribner, Richard Allen — Intervention
Amnesty smoking prevention project
$688,350 (7/90-6/93)

23. Thomas Duncan C. — Epidemiology
Modifiers of susceptibility to smoking for lung cancer
$79,948 (7/90-6/92)

24. Zlokovic, Berislav — Gen Biomed
Nicotine, tobacco smoke and the blood-brain barrier
$626,559 (7/91-6/94)

AWARD # RT 85 AWARD PERIOD FY 1990-1991

PRINCIPAL INVESTIGATOR Enrique Cadenas, Ph.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Phenols & PAH in Tobacco-Related Cardiovascular Disease.

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to identify metabolites of polycyclic hydrocarbons which are chemical components of tobacco smoke and study their effects on cardiovascular functions. Our time table begins with a series of study using model compounds of the 1-naphthol family, which are much more readily available than those of the benzo[a]pyrene family, to examine their effects on the regulation of blood vessel contraction. Both 2-methyl-1,4-naphthoquinone (K_3) and 4-amino-2-methyl-1-naphthalenol (K_5) had no vasoconstricting effects on the perfused rat mesenteric artery at concentrations between 1 to 10 uM, but greatly potentiated the vasoconstricting actions of natural vasoconstrictors vasopressin (AVP) and norepinephrine (NE). The effect of both K_3 and K_5 was reduced but not abolished by the removal of the endothelium, suggesting that their vasoaction was in part associated with inactivation or inhibition of endothelial relaxing factor(s) (EDRF). In vessels with endothelium removed, the quinones potentiated VSP- and NE-induced contraction without affecting tissue cGMP levels.

The molecular mechanisms of the vascular action of quinones were examined by studying their effects on the degree and the nature of phosphorylation of one of the key contractile proteins, i.e., myosin light chain (MLC). MLC phosphorylation was markedly increased by the quinones even though there was no change in vasotension. Nevertheless, they further increased VSP- or NE-induced MLC phosphorylation, concomitant with their potentiation of vasoconstriction. Analysis of phosphopeptides resulting from tryptic digestion of phosphorylated MLC from blood vessels perfused under various conditions clearly demonstrated that quinones increased phosphorylation of MLC at site(s) different from that induced by the natural vasoconstrictors and phosphorylation of these sites, while having no contracting effect, potentiated phosphorylation of another site which is critical for effective contraction.

AWARD # 1 RT 86 AWARD PERIOD Fiscal Year 90-91

PRINCIPAL INVESTIGATOR Clyde W. Dent, Ph.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Tobacco Cessation Among Pregnant Low Income Latino Women

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The purpose of this study is to assess and reduce the prevalence of tobacco smoking and exposure to tobacco smoke of Latino women during pregnancy. The project involves public and private prenatal health care clinics in the assessment and intervention site. The clinics involved in this study are in low income, highly urbanized areas of Southern California (Los Angeles).

Self reported tobacco exposure status and the breath samples are available from 800 women. Urine samples have been analyzed for approximately 350 patients (150 from each of the 3 county clinics). Six hundred more samples are currently being analyzed (150 from an additional county clinic and 150 from each of the three private clinics). The data reported below are from the county clinic samples.

Using self reported tobacco use status, we found 4.8% of the women (n=38) indicated any current active use of tobacco -- 1.1% indicated daily use (n=9) and 3.7% (n=29) indicated "occasional" use. The women all indicated that they smoked less than 5 cigarettes a day. An additional 6.2% (n=50) of the women indicated that they had smoked daily before they were pregnant but had recently quit (within 6 months). Over 28% of the women indicated passive exposure to tobacco.

Using a urinary cotinine/creatinine ratio as a bio-chemical marker for tobacco exposure, we found evidence of recent active smoking in 7.4% of the women (n=26) -- a difference in prevalence estimation for active smoking of 2.6% over self report. More surprisingly, only 30% (n=10) of the women with elevated cotinine levels reported recent use (24% indicated quitting recently, 12% indicated quitting long ago, and 62% indicated passive exposure only). However, the amounts of cotinine detected were consistent with very low levels of smoking. Passive exposure to tobacco as measured by the presence of any detectable urinary cotinine was 68.7% (n=240) -- a difference of 40% over the estimation by self report. Twenty-three percent (n=55) of those with detectable cotinine actually reported exposure to tobacco (active or passive). These data indicate that some patients are either unwilling to disclose or are unaware of their exposure to tobacco.

Based on existing and new American Lung Association intervention materials, we are currently in the process of developing group and one-on-one protocols for this clinic population. A field trial on the effectiveness and feasibility of a tailored anti-tobacco exposure intervention is scheduled to begin this fall.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

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Grant Awards by Institution

AWARD # 1RT 534 AWARD PERIOD 07/01/90 - 06/30/93

PRINCIPAL INVESTIGATOR JAMES H. DWYER, PH.D.

INSTITUTION UNIVERSITY OF SOUTHERN CALIFORNIA

TITLE OF PROJECT PHYSICIAN INCENTIVES AND SMOKING CESSATION EFFECTIVENESS

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Physician interventions aimed at achieving cessation of cigarette use among patients are underutilized by primary care physicians. One hypothesis explaining this underutilization is that prevention activities require physician resources but provide inadequate return under fee for service (FFS) or health maintenance organization (HMO) models of compensation.

The goal of the current study is to assess the impact of an alternative physician compensation scheme in a large corporate health plan on the effectiveness of physicians' smoking cessation interventions. This alternative scheme involves financial "prevention incentives" contingent on outcome effectiveness and cost reduction. It contrasts with FFS by providing financial incentives for preventive practice, and it contrasts with HMOs in that individual physicians are rewarded for preventive interventions that improve health in a cost-effective manner.

Cessation rates among smoking patients of salaried primary care physicians in a large corporate health plan (N = 39,000 adults) will be measured prior to as well as after implementation of the prevention incentives. It is hypothesized that: (1) smoking cessation rate (defined as self-report of three months cessation plus biochemical validation at six-month follow-up) among smoking patients will increase relative to pre-incentive periods; and (2) the increase in quit rate will exceed any increase in quit rate observed for a control sample of employees not receiving health care in the corporate clinics.

Preliminary baseline prevalence rates of "current" smokers among a random sample of the employees, retirees, and spouses are 21% for the unionized population compared to 14% for the non-represented (administration/management) population.

AWARD # KT 122 AWARD PERIOD 1990-1991

PRINCIPAL INVESTIGATOR Mario Fournier, Ph.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Diaphragm Cellular and Functional Adaptations to Emphysema

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The major objective of the research project is to assess the plasticity of the diaphragm muscle in response to the respiratory load imposed by emphysema. More specifically, its goal is to determine the time-course for cellular and functional adaptations of the diaphragm to different intensities of emphysema in the hamster model. Since the development of emphysema gradually imposes a mechanical load on the diaphragm, its pattern of activity must also change by recruiting additional motor units (a motoneuron and the subset of muscle fibers it innervates) to generate the required forces to maintain ventilation. We have described the physiological properties of diaphragm motor units in control animals and measured the diaphragm forces generated during different ventilatory behaviors. We estimated that diaphragm eupneic (during quiet breathing) forces can be generated by the recruitment of only slow-twitch and fast-twitch fatigue resistant motor units. With severe emphysema, the generation of the same eupneic forces requires the additional recruitment of more fatigable units. We also found that the force generating capacity (force/unit area) of diaphragm muscle fibers decreases with emphysema, while their average cross sectional area increases and the whole muscle becomes more resistant to fatigue. Functional adaptations have not yet been assessed at the motor unit level. Among cellular adaptations to emphysema, we found that diaphragm fibers greatly increase their capacity to generate energy for contraction through oxidative metabolic pathways. Although muscle fiber type does not change with emphysema, we are investigating possible alterations in the expressions of some contractile proteins which could also be reflected by parallel changes in the muscle shortening velocity during contraction and in the capacity of muscle fibers to utilize energy.

AWARD # RT 388 AWARD PERIOD July 1990 - June 1993

PRINCIPAL INVESTIGATOR Bevydu Gopalakrishna Ph. D.

INSTITUTION USC School of Medicine

TITLE OF PROJECT Tobacco carcinogenesis/ C-kinase oxidative activation in metastasis

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

In a human setting tobacco smoking may be a tumor promoter. Furthermore, lung cancer spreads in the body (metastasis) at an early stage while a primary tumor is still small and symptom free. This study has a long term goal to test a hypothesis that carcinogens and oxidant tumor promoters present in the tobacco smoke may have an additional role in metastasis in addition to their known role in inducing cancer. There are three primary objectives in this project. The first is to study the role of the tobacco carcinogens and tumor promoters that induce oxidative activation and/or inactivation of protein kinase C (PKC) in lung carcinoma cells. The second is to correlate this modification of PKC with the tumor cell binding to blood vessel walls. Lastly, the third goal is assessing the counteraction of antitumor promoters in altering the oxidative modification of PKC and metastasizing abilities of lung carcinoma cells influenced by tumor promoters. The first year study is focussed on understanding oxidative modification of PKC induced by tobacco tumor promoters. PKC was oxidatively activated or inactivated in lung carcinoma cells depending on the concentration and the duration of treatment with various tobacco tumor promoters (benzopyrene, diethylnitrosamines, nitric oxide, and catechol). Cigarette smoke also directly induced this modification of PKC in lung carcinoma cells. Heme may be one of the cofactors that are involved in this process. As an alternative to the use of animals, tumor cell binding studies were conducted *in vitro* using cell cultures. A bidirectional correlation was found between the tumor cell attachment to endothelium and matrix components and oxidative modification of PKC. Based on these preliminary studies a limited number of *in vivo* metastasis experiments using mice will be planned. The antitumor promoter, retinoic acid, protected PKC from oxidative modification induced by oxidant tumor promoters in intact lung carcinoma cells. Furthermore, retinoids also increased the levels of PKC in lung carcinoma cells probably by reducing the breakdown of PKC induced by an endogenous oxidation mechanism.

AWARD # 1RT555 AWARD PERIOD 1st of 3 yrs. 7/90-6/91

PRINCIPAL INVESTIGATOR Karen M. Hennigan

INSTITUTION University of Southern California

TITLE OF PROJECT Differentiating Preadolescent/Adolescent Paths to Smoking

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Abstract

This study seeks to confirm that children who begin smoking cigarettes (and drinking alcohol) in preadolescence (5th and 6th grade) are driven by different influences than the children who begin these behaviors later in adolescence. It also seeks to confirm that these children progress in their use faster, from experimental to regular use, and sustain their use longer. Predictions about the differential role of other social behaviors (antisocial behaviors, social functioning in school), aspects of the child's social environment (parent use, stressful family situations, symptoms of dysfunctional families, lack of social support, friends who use, availability of cigarettes and alcohol), and the child's own cognitive and evaluative responses and development (strength of social identity, self regard, and sensitivity to social influence) are tested.

The first of three waves of data has been collected from four cohorts of children in a California school district beginning in the 4th, 5th, 6th, and 7th grade. As additional waves of data are collected, nonequivalent comparison groups will be formed to examine use patterns and infer which correlates discriminate early use (5th & 6th grade) from later use (in 7th & 8th & 9th grade) and those who never use. Ultimately this research may lead to the development of intervention strategies tailored to the early use group which missed in current state-of-the-art smoking prevention interventions.

Early users is a target group for whom no successful theory-based intervention has yet been demonstrated. Yet it is an extremely important target group because of the increased health risk and educational sacrifice incurred by initiating smoking (and drinking) at a young age.

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Source: https://www.industrydocuments.ucsf.edu/docs/mtvl0000

AWARD # INT 351 AWARD PERIOD Year 1 (7/90-6/91) of 3 years (7/90-6/9

PRINCIPAL INVESTIGATOR David B. Winton M.D. P.I., Cheng-Min Chuong M.D. Co-PI

INSTITUTION University of Southern California

TITLE OF PROJECT Effect of Prenatal Nicotine Administration on Brain Development

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The children of mothers who smoke cigarettes during pregnancy may be adversely affected in several ways including the development of behavioral abnormalities. Nicotine, the primary component of the particulate phase of tobacco smoke, has been implicated as the "behavioral teratogen". Nicotine easily crosses the placental barrier resulting in fetal nicotine levels at least as high as in the mother. Animal models are widely accepted for neurotoxic study. Constant nicotine infusions in rats by means of osmotic minipump, result in serum nicotine levels similar to those found in human smokers. Previous studies using this system have shown that nicotine may act adversely at several critical stages of brain development.

We are using this system to study the neuroanatomical, biochemical and molecular changes resulting from prenatal exposure of the developing fetus to nicotine. Initial experiments done using a relatively high dose of nicotine (400 ng/ml) have shown intrauterine growth retardation with high perinatal mortality. The brain tissues are smaller than controls and show a characteristic degeneration primarily localized to the white matter with intracytoplasmic vacuolization. The nature of this change is being studied currently using electron microscopy and immunohistochemistry. The possibility that part of this change may be due to secondary effects from placental ischemia is under investigation. Similar changes, however, are found in established cell lines derived from human neural tumors and in primary organ cultures from neural tissues suggesting that a primary effect is likely. These changes are limited to the developing nervous system since the brains of the mother rats, exposed to the same levels of nicotine, are unaffected.

Current experiments include further analysis at levels of nicotine commonly found in smoking mothers to see if similar changes are found. *Intensive in vitro* studies are underway to establish if nicotine has effects on specific stages of neural development including neuronal precursor proliferation, neurite outgrowth, and cell migration. The results of these experiment will continue to provide important new information about brain development and the hazards of smoking during pregnancy.

AWARD # 1 RT-58 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Alan L. Hiti, Ph.D., M.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Tumor Suppressor Gene Mutations in Lung Cancer

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to evaluate the genetic changes in tumor suppressor genes in human lung carcinomas. Using archival formalin fixed, paraffin embedded tissue of the four major histologic types of lung carcinoma, this proposal utilizes state of the art molecular techniques to amplify, screen and verify abnormalities of the p53 tumor suppressor gene. This approach has widespread applicability to retrospectively detecting minute changes in any target gene sequence. Linking the types of p53 mutations to the histologic type and smoking history may provide insights into possible etiologic carcinogens. In the first year of support, the study cases have been reviewed, selected and prepared for analysis. The PCR amplification technique has been optimized to produce a single amplified product. Screening techniques have been evaluated resulting in the description and pending publication of a new, non-radioactive approach to rapidly identify mutated gene sequences. Studies to verify the presence of mutations and to identify the specific nucleotide changes are presently being evaluated and will be optimized during the second year of study.

AWARD # INT 330 AWARD PERIOD 07/01/90-6/30/9

PRINCIPAL INVESTIGATOR Florence M. Hofman, Ph.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Role of Nicotine in Endothelial Cell Function

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The goal of this study is to determine the effects of nicotine on the function of endothelial cells. We are interested in the effects of nicotine on the ability of endothelial cells to produce coagulation factors and other growth factors which are necessary for proper maintenance of the blood vessels. We found that nicotine decreases the production of the important growth factor, IL-6, which is involved in the local immune response. Nicotine also inhibits the activity of the cytokine, tumor necrosis factor alpha (TNF-α). TNF-α stimulates the coagulation process in endothelial cells, but in the presence of nicotine, this activity is reduced. This data suggests that nicotine interferes with the normal inflammatory response at the site of the blood vessels, and alters the function of the endothelial cells lining the blood vessels. These alterations could lead to more pronounced infections and lower blood clotting capabilities. We are continuing this study in order to determine the specific mechanism by which nicotine alters the cells' function. This information is essential for developing therapies to inhibit or reverse the disease processes induced by nicotine.

AWARD # RT 367 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Joseph R. Landolph, Ph. D.

INSTITUTION University of Southern California

TITLE OF PROJECT Tobacco Carcinogen Carcinogen Transformation of Human Bronchial Cells

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

In the first year of work on this grant, we made contact with a number of tissue banks and arrangements to allow us to obtain specimens of normal human bronchus from autopsy, biopsy, or surgery. We now receive specimens of normal human bronchus routinely. Secondly, we established methods to culture specimens of normal human bronchus to derive cultures of normal human bronchial epithelial (NHBE) cells. We compared Ham's F12, LDM, and LHC-9 tissue culture media, found that all these media are equally support establishment and growth of NHBE cell cultures, and chose LHC-9. We have successfully cultured NHBE cell cultures for two months. So far, we have not been able to clone these cells to establish cytotoxicity assays by plating efficiency procedures. We are working to develop these assays. After the two month period of culture, all NHBE cells then senesce. We are presently working to immortalize NHBE cells by treating them with colcemid and by transfecting them with *v-myc* and SV40 large T antigen oncogenes. Studies of tobacco carcinogen-induced transformation will then be initiated. We also conducted an experiment studying expression of RNA transcribed from the GRP78 glucose-regulated stress gene. We found that in two human bronchial epithelial tumor cell lines, A427 and cALU-3, there was abundant mRNA transcribed from this gene compared to GRP-78 mRNA levels in lymphocytes from four patients afflicted with lupus erythematosus used as negative controls. These studies indicate that these human bronchial tumor cell lines over-express GRP-78 mRNA. We also conducted experimentation with a permanent line of bronchial epithelial cells derived from Maccacus Rhesus monkey. We found that these cells grow well and clone well, yielding a four percent plating efficiency with easily identifiable, discrete colonies that are easily counted.

Finally, we found that aspirin and dexamethasone inhibited polycyclic hydrocarbon induced morphological transformation in C3H/10T1/2 mouse embryo cells and inhibited MNNG, nickel and TPA induced anchorage independence in diploid human fibroblasts. Prostaglandins, leukotrienes, and/or oxygen radicals may be involved in chemical transformation.

2023471151

Source: https://www.industrydocuments.ucsf.edu/docs/nfvl0000

AWARD # RT 140 AWARD PERIOD 7/1/90 - 6/30/91

PRINCIPAL INVESTIGATOR Stephanie J. London

INSTITUTION University of Southern California School of Medicine

TITLE OF PROJECT A Genetic Marker of Lung Cancer Risk Among Blacks And Whites

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Genetic constitution plays a role in determining lung cancer risk, perhaps by influencing susceptibility to carcinogens in tobacco smoke. Individuals vary greatly in their ability to metabolize the antihypertensive agent debrisoquine. This variation is genetically determined. Some previous evidence suggests that persons able to rapidly metabolize debrisoquine are at increased risk of lung cancer compared with slower metabolizers. In addition, debrisoquine metabolism may differ between races as well as between individuals.

We have successfully initiated a case-control study to evaluate the following hypotheses:

1. The genetically-determined ability to "extensively" metabolize debrisoquine increases the risk of lung cancer, after accounting for tobacco smoking.

2. Genetic susceptibility to lung cancer, as measured by the distribution of debrisoquine metabolism, differs between blacks and whites.

Case and control identification mechanisms have been successfully established - 25 cases and 10 controls have been enrolled. Cases are being identified at the 6 Los Angeles hospitals chosen to achieve equal enrollment of black and white cases. Controls under age 65 are selected from a tape of licensed drivers used in conjunction with another study at USC. Controls over age 65 will be selected from a tape of Medicare beneficiaries. Debrisoquine metabolism is determined by analysis of an overnight urine sample collected after administration of a small test dose of debrisoquine. In addition at no cost to the project blood samples are being analyzed for the presence of mutations in the debrisoquine metabolizer gene.

Results will be available when enrollment is complete in 1993.

AWARD # IRT90 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Dr. Amitabha Mazumder

INSTITUTION University of Southern California

TITLE OF PROJECT Novel Approach to Head and Neck Cancer Therapy

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Head and neck cancer is a significant cause of morbidity and mortality with very little progress having been made in the therapy of advanced states of this disease with chemotherapy, radiotherapy or surgery. On the other hand, this cancer lends some provocative insights into immunological therapy. A number of reports have investigated various immune aspects of these patients. These have, however, not been sorted out with respect to the role of smoking. Also, we have shown in mouse studies, that a combination of *in vivo* and *in vitro* immunizations of white cells against tumors can lead to the generation of cells that can cure the animal when infused back along with interleukin-2. We have now optimized this approach *in vitro* and are ready to initiate a clinical trial in head and neck cancer using this concept.

AWARD # IRT 220 AWARD PERIOD 7/1/90-6/30/91

PRINCIPAL INVESTIGATOR Thomas M. Mack, M.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Tobacco-Related Disease in Native California Twins

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The objective of this project is to establish a program of studies of the causes of cancers and other chronic diseases, focusing upon smoking and other environmental (i.e. non-hereditary) causes, by creating a registry of twins born and currently living in California, and obtaining base-line information about their growth and development, lifestyle and habits, diet, and medical history.

The twin pairs will be identified by linking California birth records which give evidence of multiple birth to drivers' license files, which provide current address. About half the native California twin pairs can be located in this manner; many of the rest have moved out of state or, in some cases, died. Then, using other resources, pairs of twins will be asked if they are willing to participate in detailed studies using two criteria: one based on whether the information about habits/exposures suggests that the twins differ substantially with respect to an exposure, and one based on whether the medical history indicates that their experience with disease outcomes of interest is substantially different. In the latter case, the twins will be compared to each other with respect to environmental exposures (such as smoking or passive smoking) in a search for potentially causal associations. In the pairs representing exposure discordancy, selected pairs will be followed up in a search for medical or molecular differences thought to presage the actual occurrence of cancer or chronic disease.

AWARD # 1RT515 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Mary Ann Pentz, Ph.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Effects of Social & Personal Coping Programs for Smoking Preventio

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The primary objective of this three-year project is to evaluate the relative effectiveness of two school-based programs--a personal coping program based on stress management and anger control and a social coping program based on resistance skills (social competence)--for prevention of cigarette smoking in seventh grade adolescents in three ethnically diverse school districts in Orange County, California. Secondary objectives are to evaluate: (1) the effects of intervention on use of other drugs, including smokeless tobacco, alcohol, marijuana, and cocaine; (2) the longitudinal relationships among tobacco use, stress, social competence, gang behavior, and school problem behavior over an 18 month period inclusive of three waves of measurement (pretest or baseline, 6m months, and 18 months); and (3) the strength of developmental relationships and effects of each intervention on different ethnic groups of adolescents, including Black (3.9%), Asian (9.6%), Hispanic (31.4%), and White (32.1%). In the first year, schools within each district were randomly assigned to personal coping, social coping, or a health education as usual control group (N = 16 schools); measures and the two programs were refined, the pretest was administered in late Fall, 1990, teachers were subsequently trained for program delivery, the programs were delivered and monitored for quality of implementation, and the posttest was administered six months following pretest in late Spring, 1991. Then, first year activities focused on program development and delivery. However, pretest data have been cleaned, entered, and analyzed to evaluate potential experimental group differences at pretest and cross-sectional relationships among variables. The following analyses have been conducted on pretest data: (1) chi-square analyses and t-tests on unadjusted data for experimental groups, (2) regression analyses on tobacco use, other drug use, gang behavior, and related behaviors, with school and individual as the units of analysis, and with and without adjustment for race, SES, and gender; and (3) principal components analysis and varimax and promax rotation of factors representing stress, social competence, social support, and coping constructs, followed by confirmatory factor analyses on a reduced set of factors, and (4) cross-sectional structural equation modeling of the relationships among cigarette smoking, stress, coping, social competence, and social support. Results showed no differences among experimental groups at pretest, with the exception that the personal coping group showed lower monthly alcohol use than the control group ($p < .02$). There were also few demographic group differences, with the exceptions that schools with higher proportions of Black and Asian students showed lower self and peer smoking rates (5.4% monthly smokers for Blacks, 2.9% Asian, vs. 14.6% Hispanic and 15.3% White, $p's < .02$), and that schools with higher proportions of Black and Hispanic students (each coded separately) showed the highest rates of gang participation (5.0% for Hispanic, 3.8% Black, vs. 3.1% White, 2.8% Asian; $p's < .05$). Confirmatory factor and path analyses contributing to structural equation modeling showed an acceptable model fit of data, including constructs of personal and social coping, social support, drug use, and stress ($BBNFI = .943$, $CFI = .964$). Attempts to use personal coping strategies were related to more drug use and stress at pretest; social competence was related to more drug use at pretest but less stress; and and satisfaction with social support was related to more stress. Stress and drug use were positively but not significantly related at pretest. The second year will focus on six month longitudinal analyses of program effects, differences in program effects among ethnic groups, and etiology of stress, tobacco use, other drug use, and gang behavior.

2023471152

AWARD # 1RT 423 AWARD PERIOD 7/1/90 - 6/30/93

PRINCIPAL INVESTIGATOR RONALD K. ROSS, M.D.

INSTITUTION UNIVERSITY OF SOUTHERN CALIFORNIA

TITLE OF PROJECT ENVIRONMENTAL & GENETIC RISK FACTORS FOR BLADDER CANCER

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

Cigarette smoking is the most important of the well established risk factors for bladder cancer. This study is a multifaceted approach to more precisely characterize the relationship between cigarette smoking and bladder cancer, especially to further define groups at especially high risk by virtue of this exposure and to better understand why certain populations in California (e.g., Blacks and Chinese) characterized by a high prevalence of cigarette smoking have relatively low bladder cancer rates. We are conducting a case-control interview, biochemical, and histopathologic study of bladder cancer in the high risk LA white population and the lower risk LA Black and Asian populations.

The major component of this project is a population-based case-control study involving detailed in-person interviews with bladder cancer patients and controls. Bladder cancer patients are identified by the Cancer Surveillance Program of Los Angeles County, a regional registry of the statewide California Tumor Registry. Control subjects are neighborhood controls identified by following a predetermined algorithm. The focus of the interview is on past and current tobacco use, as well as on other established or novel possible bladder cancer risk factors. Blood and urine samples will be collected on all patients and controls in years 2 and 3 of this study. These will be utilized for biochemical studies including acetylation phenotyping (n-acetyltransferase is a genetically regulated enzyme system involved in detoxification of aromatic amines - a bladder carcinogen present in cigarette smoke), aromatic amine-hemoglobin adduct measurements (a method of quantifying bioactive aromatic amine exposure), and molecular genotyping to predict debrisoquine metabolism phenotype (another purported genetic linkage to bladder cancer risk). A detailed histopathologic review is being conducted on the tumors of participating patients and on a subset of these, we are planning genetic analyses to look for specific DNA mutations induced by cigarette smoke or other possible bladder cancer risk factors. In addition to the ongoing interviewing, the laboratories have been set up for the biochemical and molecular genetic analyses and a pilot study is ongoing to standardize sample collection and laboratory procedures.

PRINCIPAL INVESTIGATOR Pradip Roy-Burman, Ph.D.

CAMPUS/INSTITUTION University of Southern California School of Medicine

AWARD # 1RT 345 AWARD PERIOD 7/1/90-6/30/91 with no-cost extension to 12/31/91

TITLE OF PROJECT Genetic aberrations in tobacco-related lung carcinogenesis

Please summarize, in language understandable by an educated layman, objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 7".

There is accumulated evidence that damage to certain gene loci, such as proto-oncogenes and growth suppressor genes, do occur in lung cancer. However, vast areas of the chromosomes, which may be frequent targets in smoking-related lung carcinogenesis, remain unexplored. We have exploited the presence of DNA repeat sequences, called variable number of tandem repeats (VNTRs), which are widely distributed and dispersed throughout the human genome, to identify closely linked genetic sequences which may be lost or rearranged in lung cancers. Substantial progress has been made during the past year. In this period, with some initial unavoidable delay, the mechanism to collect fresh lung tumors from three different hospitals was established and a total of 12 pairs of tumor/normal specimens have been obtained. Satisfactory DNA fingerprints with two different VNTR-related synthetic oligonucleotide probes were obtained, and in four pairs, gross differences between the normal and the tumor tissues (one squamous, one large cell and two adenocarcinomas) were evident. Multiple changes that were detected in the tumor DNA included differences in band intensities, loss of bands, or the appearance of novel DNA regions in the tumor DNA. The approach to clone the unique sequences adjacent to the affected tandem repeats has been improved on the basis of several trial experiments using various different protocols. The modified method appears to work for polymerase chain reaction (PCR)-based amplification of unique termini of the repeat containing sequences. From the DNAs isolated from the normal uninvolved and lung adenocarcinoma tissues of a patient, we have attempted to clone the target VNTR-linked unique sequences of fingerprint bands in the areas of 23, 13, 9.5 and 8.4 Kb, all deleted in the tumor DNA relative to the pattern of the corresponding normal DNA. Although some clones were isolated and the partial DNA sequence of two of them from the 23 Kb region determined, as yet, clones containing the target sequences remain to be isolated. Large scale cloning and screening for VNTR sequences are underway. By determining the unique sequences immediately flanking the VNTR present in the informative fingerprint bands, we should be able to assess the general issue of deletions, loss of heterozygosity or DNA rearrangements involving these or adjacent sequences in smoking-induced lung carcinogenesis.

AWARD # 1RT 345 AWARD PERIOD 07/01/90 - 06/30/91

PRINCIPAL INVESTIGATOR Richard Allen Scribner

INSTITUTION University of Southern California

TITLE OF PROJECT Agency Smoking Prevention Project

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The study is designed to observe the adoption of certain smoking behaviors among immigrating Latinos which are associated with U.S acculturation. These include an increase in percentage of new smokers among women and an increase in the number of cigarettes smoked per day among both men and women. The study will follow a panel of adult Latino immigrants for two years with 3 annual surveys.

During the first year approximately 890 Latino immigrants were recruited. Preliminary data have been compiled on the first 478 participants. The data are consistent with surveys of other Latino immigrant populations (see Table 1). With regard to smoking status the prevalence of smoking in the sample is lower than data from surveys of Latinos in the general population. In addition, the gender difference in smoking status, 33.9% versus 9.1%, is greater than has been previously reported. These findings are consistent with an intra-generational affect of acculturation on smoking status among women.

Table 1. Preliminary statistics

	%
Ethnicity of Origin (n=478)	
Mexican	94.2
Latin American	4.2
North American	1.6
Age (years)	
less than 29	68.8
over 30	31.3
Sex	
Male	63.0
Female	36.9
Years of Education	
Less than 12	88.9
College	11.1
Annual Income	
< $10,000	52.3
> $10,000	47.7
Smoking Status (Last 7 days)	
Total Smokers	26.6
Male Smokers	33.9
Female Smokers	9.1
Acculturation (1=Mex, 5=US)	
1.0-1.9	75.0
2.0-2.9	17.4
> 3.0	8.6

The majority of the sample had acculturation scores ranging from 1.0 to 1.9 on a index ranging from 1 to 5. A factor analysis of a 12 item acculturation scale used in the survey replicated the findings of Marin et. al. who surveyed a cross section of the Latino population to validate the scale. However, the factor "Media" accounted for a greater amount of variation of the scale in our sample as opposed to the factor "Language Use" in Marin's sample. This suggests that processes related to media usage account for a greater amount of the variation in acculturation score among the immigrant population, whereas processes related to language use account for the majority of the variation among the general Latino population.

AWARD NO. 1RT190 AWARD YEAR 1 X 2 ___ 3 ___

PRINCIPAL INVESTIGATOR Duncan Thomas, Ph.D.

INSTITUTION University of Southern California

TITLE OF PROJECT Modifiers of Susceptibility to smoking for lung cancer.

Please summarize, in language understandable to an educated lay person, the objectives of this project and the progress to date toward achievement of the specific aims. Print the abstract in the box.

The objectives of this research were to re-analyse two existing data-sets to explore factors that potentially modify the association between lung cancer and smoking.

(1) The first dataset was a case-control study of lung cancer in women, with data on lung cancer and smoking in first degree relatives. We proposed to analyze this dataset to determine if the strong familial risk for lung cancer previously reported may be explained by correlation in smoking among family members, or by a correlation in their susceptibility to lung cancer. Because of limited smoking data on family members, a large portion of time has been spent developing a model for imputing missing smoking data. Initial analyses of these data are currently in progress.

(3) The second dataset was a cohort study of lung cancer in uranium miners with longitudinal data on smoking and radon exposure. We proposed to analyze these data to determine if the previously observed interaction between radon and smoking can be further refined by incorporating temporal factors, and to assess the effect of random error in measurement of radon exposure on these results. Much of the effort in the first year was spent in initial data preparation, as extensive data cleaning and edits were necessary. For efficiency of analyses, a nested case-control sample of the cohort was selected with 15 controls per case, resulting in an analysis data set with 1873 subjects. Descriptive models are currently being fitted; initial results indicate that simultaneous smoking and radon exposure confer a more than multiplicative risk of lung cancer, whereas smoking preceding radon exposure, or vice versa, produces a less than multiplicative effect.

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Source: http://www.industrydocuments.ucsf.edu/docs/mnw0000

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Grant Awards by Institution

Veterans Medical Research Foundation of San Diego

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

1 $291,601

b) The subject of research grants by academic discipline:

Cardiovascular Disease = 1

c) The relationship between State and Federal funding for tobacco research:

0

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

1 $291,601

g) The number and species of animals used in research:

Pigs = 90/year

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

1 $291,601

Grant Recipient(s):

1. Ito, Bruce R. Cardiovascular
Complement mediated cardiac ischemia & thromboxane release
$291,601 (7/90-6/93)

AWARD # 1-RT 400 AWARD PERIOD July 1, 1990 - June 30, 1991

PRINCIPAL INVESTIGATOR Bruce R. Ito

INSTITUTION Veterans Medical Research Foundation of San Diego

TITLE OF PROJECT Complement Mediated Cardiac Ischemia & Thromboxane Release

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The loss of blood supply to the heart muscle ("ischemia") occurring with coronary artery disease eventually leads to heart attack and is a major threat to the health of American adults. Cigarette smoking is a major risk factor linked to an increased incidence of heart disease, and remains a significant health problem. With the advent of clinical procedures to restore blood flow to ischemic heart, came the finding that a significant portion of the heart injury is linked to a local inflammatory response triggered by ischemia. Inflammation causes further injury in addition to the simple lack of blood flow to the heart muscle. We have developed an experimental model of one of these inflammatory pathways ("complement pathway") which is now know to be activated with heart attack in humans. This pathway, which in its normal role is essential in the host-defense against bacteria, involves the sequential modification of various proteins in blood to several biochemically active agents. One particular end-pathway agent, C5a, (activated complement-fifth protein): (1) has deleterious effects on coronary vessels, (2) attracts potentially damaging white blood cells (WBC) to the heart, and (3) produces secondary agents (ie. thromboxane, TX) which can themselves cause ischemia. Understanding these actions of C5a may yield clinically useful strategies to limit injury resulting from heart attack. In the past few years we have described these cardiac effects of C5a in a controlled experimental model which utilizes an anesthetized swine preparation in which coronary blood flow, heart contraction, and chemical release into coronary venous blood are measured. The objectives of the present project are to investigate the interactions of the various effects of C5a described above. Where does the TX release caused by C5a come from? Is this from blood cells (ie. platelets, or WBC)? Are WBCs required for the deleterious effects of C5a on coronary blood flow? Is there any indication that inflammatory cells that normally reside in the coronary vessels (ie. mast cells) are involved in this response to C5a? Is myocardial ischemia itself a stimulus for the release of TX from the heart? Does the restoration of blood flow to the heart after ischemia cause more TX to be released? Although, we have been delayed in the activation of the TDRP grant supporting the exploration these questions, we do have some preliminary results. Platelets nor WBCs appear to be required for either the myocardial ischemia or the enhanced production of TX caused by C5a. Chemical depletion of both of these cell types from blood does not seem to alter the cardiac response to C5a. A chemical marker of cardiac mast cell activation appears to be released into coronary venous blood in the presence of C5a. We will continue the investigation of these questions.

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Western Consortium for Public Health

a) The number and dollar amount of research grants, including the amount allocated to indirect costs:

2 $215,412

b) The subject of research grants by academic discipline:

Epidemiology = 1
Public Health, Public Policy, and Economics = 1

c) The relationship between State and Federal funding for tobacco research:

Other State = $10,000
Federal = $18,000

d) The relationship between each project and the overall strategy of the research program :

see d) in Summary Data above

e) A summary of research findings:

see abstract(s) below

f) The number and dollar amounts of research grants that involved the use of animals:

0

g) The number and species of animals used in research:

N/A

h) The number and dollar amounts of research grants that utilized animal alternative methods as defined by the United States Office of Technology Assessment's 1986 report entitled "Alternatives to Animal Use in Research, Testing, and Education":

N/A

Grant Recipient(s):

1. *Moskowitz, Joel* *Pub Health*
Smoking ordinances, passive smoking and smoking cessation
$151,607 (7/91-6/92)

2. Van den Berg, Barbara Epidemiology
Precursors and correlates of smoking in adolescents
$63,805 (7/90-6/92)

AWARD # Grant No. RT-49 AWARD PERIOD 1990-1992 (Year 01)

PRINCIPAL INVESTIGATOR Barbara J. van den Berg, M.D.

INSTITUTION Western Consortium for Public Health

TITLE OF PROJECT Precursors and Correlates of Smoking in Adolescents

Please summarize, in language understandable by an educated layman, the objective of this project and the significant findings resulting from the work. Limit the abstract to a space 6" by 5.5".

The main objectives of this project are to investigate health, health habits, physical, cognitive, and psychosocial development of young women and young men who adopted the habit of smoking cigarettes during their adolescent years. The basic data are derived from the data sets of the Child Health and Development Studies, which started in 1960 and included a study population of 20,000 newborns and their parents.

The current project relates to a subcohort of about 2,000 young people, with information on the growth and development from birth to young adulthood, who also participated in developmental examinations at 5 years, at 10 years, and at adolescence, when they were 15-17 years old. During the eight months covered by this project, we made progress with the analyses of spirometric measurements and of blood pressure measurements of the smoking and nonsmoking adolescents. The smoking habits of young people can be considered to be a marker for behavior that may have consequences for the health or well-being of the young people. One of these is use and abuse of alcohol. We found that among the smoking adolescent girls, 42% took alcoholic drinks once or more often per week, while this percentage was only 11% for the nonsmoking girls. Another observation, derived from the medical records, was that one-third of smoking girls had their first pregnancy before age 20, while only 10% of the nonsmoking girls had their first pregnancy before age 20.

We have given great effort to the updating of the addresses of the young women of the project. Follow-up investigations are in progress for these young women, who are now in their twenties. We cooperated with investigators from the University of North Carolina, who developed the protocols. When these studies are completed, the data on changes in smoking habits, in relation to health, e.g., incidences of respiratory diseases, and other health-related factors, can be investigated.

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Grant Awards by Institution

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4

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